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ANAPHYLACTOGENIC PROPERTIES OF MILK

IMMUNOCHEMISTRY OF THE PURIFIED PROTEINS AND ANTIGENIC CHANGES RESULTING FROM HEAT AND ACIDIFICATION

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Hypersensitivity to milk is a relatively common cause of food allergy. It is most frequently observed in infancy, but occurs in adult life as well. Certain sensitive persons cannot take raw or pasteurized milk without ill effects, but can generally tolerate milk modified by heat. The reason for the tolerance for modified milk is not well understood. The problem was therefore reopened to determine what antigenic changes result when milks are boiled, evaporated, superheated, dried or acidified, in order better to explain the greater tolerance.

IMMUNOCHEMISTRY OF PURIFIED PROTEINS OF MILK

It is essential to work with pure proteins. Extensive studies have been made on the immunologic properties of the proteins of raw milk but relatively few on those of heated milks, and the few studies have been carried out on crude separations of casein and whey. None of the commercial purified caseins or purified milk proteins that we obtained from various laboratories or the simple separations of casein and whey were of any value, for our preliminary experiments showed them to be biologically impure.

Preparation of the Protein Fractions.—The various fractions of the milk proteins were prepared by the courtesy of Dr. A. H. Palmer, of the department of chemistry. The fractions which we have employed will be designated as casein, lactoglobulin and lactalbumin. It is known that both lactoglobulin and casein when prepared by the standard methods are capable of fractionation into two or more chemically and, presumably, immunologically distinct fractions.[1] At the

This work has been aided by a special grant from the National Research Council.

From the Departments of Pediatrics and Immunology, University and Bellevue Hospital Medical College, New York University, and the Children's Medical Division, Bellevue Hospital.

Mary Adams, M.D., and Milton Redish, B.A., gave technical assistance in the laborious and painstaking feeding experiments.

1. Wells, H. G., and Osborne, T. B.: Anaphylaxis Reactions with Purified Proteins from Milk, J. Infect. Dis. **29**:200, 1921.

same time, there is evidence that the unfractionated casein and lactoglobulin, though they are not chemical individuals, are immunologically distinct from one another. It was our object to determine if a strict separation of one from the other by chemical means could be established by drastic biologic tests. The lactalbumin fraction of milk, on the other hand, has generally been regarded as a single protein, though few studies of the fraction have been made. Dr. Palmer [2] has shown, however, that this is not true, since he has been able to separate from it a crystalline globulin corresponding in amount to 60 per cent of the protein in the albumin fraction. In the majority of the work we have been content to compare the antigenic specificities of the whole lactalbumin with those of various treated and untreated milks and of the casein. A few tests, however, have been made of the specificity of the crystalline globulin of Palmer and of two arbitrary fractions of the noncrystallizable residue of the lactalbumin fraction.

Casein: This was prepared by the method of Van Slyke and Baker,[3] with the modification that the washing of the casein was done with a 2 per cent solution of sodium chloride instead of with water. This was done in the hope of effecting a more complete separation of lactoglobulin from the casein. The washed casein was dissolved by dilute sodium hydroxide under such conditions that the p_H was not allowed to rise above 8. The solution was reprecipitated by the method of Van Slyke and Baker, was redissolved twice more and was finally dissolved by a solution of sodium hydroxide to a p_H of 7. The solution was dialyzed three days before use.

Globulin: The filtrate from the casein was adjusted to p_H 6.5 with sodium hydroxide, and an equal volume of a saturated solution of ammonium sulphate was added slowly and with stirring. The precipitate was removed, washed with a half-saturated solution of ammonium sulphate and redissolved in water. The separation and washing were repeated three times. The final precipitate was dissolved in water (sufficient salt already being present) and dialyzed at p_H 7 in order to remove the ammonium sulphate. During the dialysis some globulin was precipitated, and this was finally redissolved with the addition of a little solution of sodium chloride.

Lactalbumin: The filtrate from the globulin precipitate was saturated with ammonium sulphate, and the precipitate was removed and redissolved in water. The salting-out process was repeated three times. The final precipitate was dissolved in water, the p_H was adjusted to 5.8 and the solution was dialyzed until the dialysate after forty-eight hours gave no sulphate reaction. A slight separation of an oily precipitate occurred. This was removed.

Crystalline Globulin (Lactalbumin Fraction 3): This was a preparation of the crystalline globulin obtained from the purified albumin fraction.[2]

Lactalbumin Fraction 2: To the mother liquor (which is salt-free) from the crystalline globulin was added 20 Gm. of anhydrous disodic sulphate to each 100 cc. The precipitate was removed, redissolved and reprecipitated three times. A solution of the final precipitate, after dialysis, was used in the tests.

Lactalbumin Fraction 4: This constituted the residual protein of the lactalbumin fraction after the removal of the crystalline globulin and fraction 2. It gave

2. Palmer, A. H.: Preparation of a Crystalline Globulin from the Lactalbumin Fraction of Cow's Milk, J. Biol. Chem. **104**:359, 1934.

3. Van Slyke, L. L., and Baker, J. C.: The Preparation of Pure Casein, J. Biol. Chem. **35**:127, 1918.

no trace of a precipitate with disodic sulphate until 28 Gm. of the salt had been added to 100 cc. of its solution. It was completely precipitated on the addition of 34 Gm., and was dialyzed before use.

The materials used in the experiments were raw skimmed milk, bovine serum, casein, whole lactalbumin, crystalline globulin and the two lactalbumin fractions.

Immunologic Methods Used.—The biologic purity of the substances was tested by the anaphylactic method. The precipitin method was not found to be expedient because of the opalescence of some of the preparations, and the Schultz-Dale method was not used because of its unreliability.[4]

Guinea-pigs were used in the experiments. All animals were obtained from a reliable source and were raised on a known dietary which did not contain the proteins under investigation. It has been shown by Rosenau and Anderson [5] and many others [6] that animals can be sensitized through feeding and also that the fetus can be sensitized to the food ingested by the mother.[7] No animal manifested anaphylactic reactions to the first sensitizing injection, which served as a control in each animal.

The animals were sensitized by the intraperitoneal route unless otherwise indicated. An interval of three weeks or more elapsed between the sensitizing and the intoxicating injection. The intravenous route was used in all instances for the intoxicating injection, because no intoxicating dose is valid in determining the degree of shock unless the intravenous route is the portal of entry. The control shock dose, when used, was given about one hour later.

In studies on the determination of the purity of antigenic substances a "double shock" or "control shock injection" is essential. If it is desired to demonstrate the absence of protein B in protein A, one should sensitize with A and shock with B. If a negative or doubtful reaction ensues, a second shock or control injection of the original protein should be given. A positive reaction to the second shock injection would then confirm that A was virtually free from B.

In cross-testing, adequate sensitizing doses must be used, because a larger amount is necessary to produce cross-sensitization to a heterologous protein containing the common antigen.

In determining specificity it is imperative that every precaution be taken to avoid contamination with the various antigens used in the experiments. Numerous papers on anaphylactic specificity do not take cognizance of this precaution. All glassware, after thorough washing, was kept in concentrated cleaning solution for twenty-four hours, and all apparatus was thoroughly sterilized before an antigen was used.

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4. Ratner, B., and Gruehl, H. L.: Comparison of Methods Used in the Study of Anaphylaxis, J. Lab. & Clin. Med. **16**:1069, 1931.

5. Rosenau, M. J., and Anderson, J. F.: A Study of the Cause of Sudden Death Following the Injection of Horse Serum, Public Health Service, Hyg. Lab. Bull., 1906, no. 29, p. 67.

6. A complete bibliography is given in Ratner, B., and Gruehl, H. L.: Passage of Native Proteins Through the Normal Gastro-Intestinal Wall, J. Clin. Investigation **13**:517, 1934.

7. Wells, H. G.: Studies on the Chemistry of Anaphylaxis: III. Experiments with Isolated Proteins, Especially Those of the Hen's Egg, J. Infect. Dis. **9**:147, 1911. Ratner, B.: Placental Transmission of Alimentary Anaphylaxis, Proc. Soc. Exper. Biol. & Med. **30**:88, 1932.

Experimental Data.—Raw Milk: In determining the optimum sensitizing dose, it was found that 1 cc. of milk did not sensitize as regularly as did 5 cc. (table 1). The latter dose was therefore used for the sensi-

TABLE 1.—*Comparison of Effects of Sensitizing Doses of Raw Milk of One and Five Cubic Centimeters*

Total Number of Animals	Sensitizing Dose, Raw Milk, Cc.	Shock Injection, 1 Cc.*		Positive Reactions, per Cent
		Positive	Negative	
45	1†	25	20	55
45	5†	38	7	84

* The injections were administered intravenously.
† The injections were administered intraperitoneally.

TABLE 2.—*Reactions of Animals Sensitized to Raw Milk (Five Cubic Centimeters Intraperitoneally)*

Number of Animal	Reaction to Shock Dose*	Number of Animal	Reaction to Shock Dose*
	Casein, 0.028 Gm.		**Bovine Serum, 1 Cc.**
1	++++	33	++++
2	++++	34	++++
3	++++	35	++++
4	++++	36	+++
5	++++	37	+++
6	++++	38	+
7	++++	39	+
8	++++	40	0
9	+++	41	0
10	+++		
11	+++		
12	+++		**Lactalbumin Fractions, 0.018 Gm.**
13	++		
14	++	42	++++
15	+	43	++++
16	+		
17	0		
18	0		**Lactalbumin Fractions, 0.0292 Gm.**
19	0		
	Lactalbumin, 0.016 Gm.	44	++++
		45	++
20	++++		
21	++++		
22	++++		**Crystalline Globulin, 0.0136 Gm.**
23	++++		
24	++++	46	++++
25	++++	47	+++
26	+++		
27	+++		
28	++		
29	+		
30	+		
31	0		
32	0		

* All the shock doses were administered intravenously.

tizing injection. Raw milk crossed regularly with casein, lactalbumin, bovine serum, crystalline globulin and the lactalbumin fractions (table 2).

Casein: Animals sensitized to casein responded with regularity to a shock injection of casein or of raw milk (table 3). When casein was crossed with lactalbumin, a great majority of the animals showed an

absence of cross-relation. Although three animals died as a result of the cross-injection, the majority showed negative reaction to lactalbumin and were highly sensitized to the original substance. This indicated that absolute purity is difficult if not impossible to obtain. The casein was purified to a high degree, as shown by the rigorous tests. When casein was crossed with bovine serum the negative results gave further indication of its purity.

TABLE 3.—*Reactions of Animals Sensitized to Casein (0.085 Gm. Intraperitoneally)*

Number of Animal	Reaction to Shock Dose*	Reaction to Control Shock Dose	Number of Animal	Reaction to Shock Dose*	Reaction to Control Shock Dose
	Casein, 0.035 Gm.			Lactalbumin, 0.016 Gm.	Casein, 0.035 Gm.
1	++++		29	++++	
2	++++		30	++++	
3	++++		31	++++	
4	++++		32	++	++++
5	++++		33	+	++++
6	++++		34	0	++++
7	+++		35	0	++++
8	+++		36	0	++++
9	+++		37	0	++++
10	+++		38	0	+++
11	++		39	0	+++
12	++		40	0	+++
13	+		41	0	+++
14	+		42	0	++
15	+		43	0	++
16	+		44	0	+
17	+		45	0	+
18	0		46	0	+
19	0				
				Bovine Serum, 1 Cc.	Casein, 0.014 Gm.
	Raw Milk, 1 Cc.		47	+++	++++
20	++++		48	+++	+++
21	++++		49	+	++++
22	++++		50	+	+++
23	+++		51	+	+++
24	+++		52	0	+++
25	++		53	0	+++
26	+		54	0	++
27	+		55	0	+
28	+		56	0	+
			57	0	+
			58	0	+

* The shock doses and control shock doses were administered intravenously.

Lactoglobulin.—It is practically impossible to obtain a lactoglobulin preparation free from lactalbumin to such a degree that its purity is comparable to that of the casein and lactalbumin. In a few experiments we used lactoglobulin, while in others, in view of the work of Crowther and Raistrick,[8] bovine serum was used as representative

8. Crowther, C., and Raistrick, H.: A Comparative Study of the Proteins of the Colostrum and Milk of the Cow and Their Relations to Serum Proteins, Biochem. J. **10**:434, 1916.

of some part of the lactoglobulin fraction. In table 4 it is seen that bovine serum crosses with raw milk. This demonstrates the presence of a common protein. There was a moderate cross-sensitization with the lactalbumin and none with the casein.

Lactalbumin: Lactalbumin is highly anaphylactogenic when tested against itself and against raw milk (table 5). When crossed with casein,

TABLE 4.—*Reactions of Animals Sensitized to Lactoglobulin*

Number of Animal	Reaction to Shock Dose†	Reaction to Control Shock Dose
Sensitizing Dose,* Lactoglobulin, 0.05 Gm.		
	Lactalbumin, 0.016 Gm.	
1	++++	
2	++++	
3	++++	
4	++++	
5	+	
6	+	
	Bovine Serum, 1 Cc.	
7	++++	
8	++++	
9	+++	
10	+++	
11	+	
12	+	
13	+	
14	+	
Sensitizing Dose, Bovine Serum, 5 Cc.		
	Bovine Serum, 0.5 Cc.	
15	++++	
16	++++	
	Bovine Serum, 1 Cc.	
17	++++	
18	++++	
19	++++	
	Raw Milk, 1 Cc.	
20	++++	
21	++++	
22	+++	
23	+++	
Sensitizing Dose, Bovine Serum, 5 Cc.		
	Raw Milk, 1 Cc.	
24	+++	
25	+++	
26	+++	
27	+++	
28	+++	
29	++	
30	++	
31	++	
32	++	
33	++	
34	+	
35	+	
36	+	
37	+	
38	+	
39	0	
40	0	
41	0	
42	0	
43	0	
44	0	
	Lactalbumin, 0.016 Gm.	**Bovine Serum, 0.5 Cc.**
45	++++	
46	++	++++
47	0	+++
48	0	+
49	0	+
	Casein, 0.028 Gm.	**Bovine Serum, 1 Cc.**
50	0	+++
51	0	+++
52	0	++
53	0	++
54	0	+
55	0	+

* The sensitizing doses were administered intraperitoneally.
† The shock doses and the control shock doses were administered intravenously.

lactalbumin gave no reactions; so it is presumably free from casein. There were only two negligible cross-reactions against eighteen negative reactions. In each instance the animal was subsequently proved highly sensitive to lactalbumin. The majority of animals sensitized to lactalbumin failed to react to bovine serum, although three gave reactions which suggested a trace of globulin in the lactalbumin. Some common factor, therefore, must be present.

IMMUNOCHEMISTRY OF EVAPORATED AND MODIFIED MILKS

The foregoing observations show that each of the protein fractions is a powerful antigen. Wherein are the anaphylactogenic properties of the proteins affected by such modifications as heating, drying or acidification? Are there any changes in specificity?

TABLE 5.—*Reactions of Animals Sensitized to Lactalbumin (0.078 Gm. Intraperitoneally)*

Number of Animal	Reaction to Shock Dose*	Reaction to Control Shock Dose	Number of Animal	Reaction to Shock Dose*	Reaction to Control Shock Dose
	Lactalbumin, 0.016 Gm.			Casein, 0.028 Gm.	Lactalbumin, 0.016 Gm.
1	++++		43	+++	++++
2	++++		44	++	++++
3	++++		45	0	++++
4	++++		46	0	++++
5	++++		47	0	++++
6	++++		48	0	++++
7	++++		49	0	++++
8	++++		50	0	++++
9	++++		51	0	++++
10	++++		52	0	++++
11	++++		53	0	++++
12	++++		54	0	++++
13	++++		55	0	++++
14	++++		56	0	++++
15	++++		57	0	++++
16	++++		58	0	++++
17	++++		59	0	+++
18	++++		60	0	+++
19	++++		61	0	+
20	++++		62	0	+
21	++++				
22	++++				
23	++++				
24	+++				
25	+++				
26	+				
27	+				
28	0				
29	0				
	Raw Milk, 1 Cc.			Bovine Serum, 1 Cc.	
30	++++		63	++++	
31	++++		64	+++	++++
32	++++		65	++	+++
33	++++		66	0	++++
34	++++		67	0	++++
35	++++		68	0	++++
36	++++		69	0	++++
37	+++		70	0	+++
38	+++		71	0	+
39	+++				
40	++				
41	+				
42	0				

* The shock doses and control shock doses were administered intravenously.

Materials Used.—Evaporated Milk: The preparation was diluted with an equal amount of water to make it comparable to whole raw milk.

Smaco 303: The preparation was removed from the can and used without dilution, as no concentration of the milk is made in the process of manufacture.

Boiled Milk: Skimmed raw milk was boiled for four hours in a large Ehrlenmeyer flask loosely plugged with cotton to prevent evaporation. During the process of boiling the milk was kept stirred by shaking.

Acidified Milk: All milks were acidified by the addition of an 85 per cent solution of lactic acid, U. S. P., in the proportion of 6 cc. per liter, according to the method of Marriott.[9]

Dried Milks: Dryco, similac and klim were diluted with water to the proportion of whole milk.

TABLE 6.—*Reactions of Animals Sensitized to Evaporated Milk (5 Cc. Intraperitoneally)*

Number of Animal	Reaction to Shock Dose*	Reaction to Control Shock Dose
	Evaporated Milk, 1 Cc.	
1	++++	
2	++++	
3	++++	
4	+++	
5	+++	
6	++	
7	++	
8	+	
9	0	
10	0	
	Raw Milk, 1 Cc.	
11	++++	
12	++++	
13	+++	
14	0	
15	0	
16	0	
	Casein, 0.028 Gm.	
17	++++	
18	++++	
19	++++	
20	++++	
21	+++	
22	0	
	Lactalbumin, 0.016 Gm.	
23	++++	
24	++++	
25	++++	
26	++++	
27	++++	
28	++++	
29	++++	
30	++++	
31	++++	Evaporated Milk, 1 Cc.
32	++++	
33	++++	
34	+++	++++
35	+	++++
36	+	++++
37	0	++++
38	0	+++

Number of Animal	Reaction to Shock Dose*	Reaction to Control Shock Dose
	Bovine Serum, 1 Cc.	Evaporated Milk, 1 Cc.
39	++++	
40	+	++++
41	+	++++
42	0	++++
43	0	++++
44	0	++++
45	0	++++
46	0	++++
47	0	++++
48	0	++++
49	0	++++
50	0	++++
51	0	++++
52	0	++++
53	0	++++
54	0	++++
55	0	++++
56	0	++++
57	0	++++
58	0	++++
59	0	++++
60	0	++++
61	0	+++
62	0	++
	Crystalline Globulin, 0.0136 Gm.	
63	++++	
64	++++	
65	++++	
66	+++	
67	+++	
68	+	++
	Lactalbumin Fractions, 0.0145 Gm.	
69	++++	
70	++++	
71	++++	
72	++++	
73	+++	
74	+++	
75	+	++++
	0.018 Gm.	
76	++++	
77	+++	
78	+++	

* The shock doses and control shock doses were administered intravenously.

All the modified milks used were prepared fresh before each experiment and were never used on subsequent days. This obviated any chemical change which might result from standing.

9. Marriott, W. M.: Infant Nutrition, St. Louis, C. V. Mosby Company, 1930.

Experimental Data.—Evaporated Milk: In table 6 it will be noted that in animals sensitized to evaporated milk shock is regularly produced by that substance. Hence evaporated milk is anaphylactogenic. When crossed with raw milk, the anaphylactogenic properties are still present.

TABLE 7.—*Reactions of Animals with Evaporated Milk as Shock Agent (1 Cc. Intravenously)*

Number of Animal	Reaction to Sensitizing Dose*	Reaction to Control Shock Dose†
	Raw Milk, 5 Cc.	Raw Milk, 1 Cc.
1	++++	
2	++++	
3	++++	
4	++++	
5	++++	
6	++++	
7	+++	+++
8	+++	+++
9	++	++++
10	++	++
11	+	+
12	+	+
	Casein, 0.140 Gm.	Casein, 0.014 Gm.
13	++++	
14	++++	
15	++++	
16	++++	
17	++++	
18	+++	+++
19	+++	+++
20	+	+
21	+	+
	Bovine Serum, 5 Cc.	Raw Milk, 1 Cc.
22	+++	++++
23	+++	+++
24	+	++++
25	+	+++
26	+	++
27	0	+++
28	0	+++
29	0	+++
30	0	++
31	0	++
32	0	+
33	0	+
34	0	+

Number of Animal	Reaction to Sensitizing Dose*	Reaction to Control Shock Dose†
	Lactalbumin, 0.078 Gm.	Lactalbumin, 0.016 Gm.
35	+	++++
36	+	++++
37	+	+++
38	+	+++
39	0	++++
40	0	++++
41	0	++++
42	0	++++
		Raw Milk, 1 Cc.
43	0	++++
44	0	++++
45	0	++++
46	0	++++
47	0	++++
48	0	++++
49	0	++++
50	0	++++
51	0	++++
52	0	+++
53	0	++
54	0	+
	Crystalline Globulin, 0.027 Gm.	Raw Milk, 1 Cc.
55	0	++++
56	0	++++
57	0	++++
58	0	++++
59	0	+‡
60	0	+‡
	Lactalbumin Fractions, 0.058 Gm.	Raw Milk, 1 Cc.
61	0	++++
62	0	++++
63	0	++++
64	0	+++
65	0	++
66	0	0
	0.036 Gm.	
67	0	++++
68	0	++++
69	0	++++
70	0	++++
71	0	++‡
72	0	0‡
73	0	0‡

* The sensitizing doses were administered intraperitoneally.
† The control shock doses were administered intravenously.
‡ A subsequent shock injection was given with the sensitizing fraction, and in no instance did they show more severe symptoms than with raw milk.

Evaporated milk crossed with casein gave positive reactions. It is generally agreed that the physical properties of casein are not affected by heat, and we found that the specific reactions persist. Evaporated milk crossed with pure lactalbumin also gave positive reactions. Lactal-

bumin, which is known to lose its solubility, a change thought to be chemical, for some reason retained its anaphylactogenic properties. In four animals, however, the sensitization to lactalbumin was diminished, for the control shock injection of evaporated milk showed them markedly sensitive. Evaporated milk crossed with bovine serum gave negative results. This is evidence that the anaphylactogenic properties of the common globulin are modified in evaporated milk. The animals showing a negative reaction to bovine serum proved to be highly sensitive to the control shock injection of evaporated milk. Thus, evaporated milk retains the property of sensitizing not only to itself to raw milk and casein, but also, to a large extent, to lactalbumin. The sensitizing

TABLE 8.—*Reactions of Animals Sensitized to Smaco 303 (5 Cc. Intraperitoneally)*

Number of Animal	Reaction to Shock Dose*	Reaction to Control Shock Dose	Number of Animal	Reaction to Shock Dose*	Reaction to Control Shock Dose
	Smaco 303, 0.5 Cc.			Casein, 0.028 Gm.	
1	++++		13	+++	
2	++++		14	++	
3	++++			Lactalbumin, 0.016 Gm.	
	Raw Milk, 1 Cc.		15	++++	
4	++++		16	++++	
5	++++		17	++++	
6	+++		18	+++	
7	++		19	+++	
8	+		20	+	
	Whey, 1 Cc.			Bovine Serum, 0.5 Cc.	Smaco 303, 0.5 Cc.
9	++++				
10	++++		21	0	++++
11	++++		22	0	++++
12	+++		23	0	+++

* The shock doses and control shock doses were administered intravenously.

property of globulin is largely gone. It is further shown that evaporated milk retains its sensitizing power to the crystalline globulin and the purified lactalbumin fractions. In view of the results it appears that evaporated milk can still sensitize to raw milk and its isolated pure fractions.

We then reversed the order of sensitization and shock, using evaporated milk as a shock agent against the isolated proteins, which we believed might demonstrate some change in its antigenic properties. According to table 7 evaporated milk produces shock in animals sensitized to raw milk or to casein. However, when bovine serum, lactalbumin, crystalline globulin or the purified lactalbumin fractions were used for sensitization, a shock injection of evaporated milk failed to produce a reaction in all but a few instances, and in these the reaction was negligible, whereas after a second shock dose of raw milk the animals, in the majority of instances, promptly died in anaphylaxis.

Smaco 303 (a So-Called Hypo-Allergic Milk): Smaco 303 regularly sensitizes to itself, raw milk, purified casein and lactalbumin, but has lost its ability to sensitize to bovine serum (table 8). When the order is reversed (table 9), smaco 303 regularly reacts as a shock agent in animals sensitized to raw milk. There was a greater percentage of reactions in animals sensitized to lactalbumin when smaco 303 was used as a shock agent than when evaporated milk was used (table 7), although there was a diminution of its intoxicating properties.

Milk Boiled for Four Hours: Animals sensitized to milk boiled for four hours manifested reactions similar to those sensitized to evaporated milk.

Acidified Milks: Acidified raw milk was shown to be highly anaphylactogenic.

TABLE 9.—*Reactions of Animals with Smaco 303 as Shock Agent (1 Cc. Intravenously)*

Number of Animal	Reaction to Sensitizing Dose* Raw Milk, 5 Cc.	Reaction to Control Shock Dose Raw Milk, 1 Cc.	Number of Animal	Reaction to Sensitizing Dose* Lactalbumin, 0.078 Gm.	Reaction to Control Shock Dose† Raw Milk, 1 Cc.
1	++++		12	+++	++++
2	++++		13	+++	++++
3	++++		14	++	++++
4	++++		15	+	++++
5	++++		16	+	++++
6	++++		17	+	++++
7	++++		18	0	++++
8	++++		19	0	++++
9	+++	++++	20	0	++++
10	0	0	21	0	++++
11	0	0	22	0	++++
			23	0	++++
			24	0	0
			25	0	0

* The sensitizing doses were administered intraperitoneally.
† The control shock doses were administered intravenously.

Dry Milks: In this group were dryco, klim and similac, all of which were found to be highly anaphylactogenic.

Boiled, acidified and dried milks could not be used for intravenous shock injections because of their physical character (precipitated flocculi), which produced anaphylactoid reactions.

SENSITIZATION TO RAW AND TO MODIFIED MILKS THROUGH FEEDING

The following experiments were carried out to determine the difference in anaphylactogenic properties of raw and modified milks when fed. The animals were all fed under normal conditions without the use of a stomach tube. Regardless of the type of milk used, the same dose was given to each animal.

The main principles underlying the passage of antigens through the normal gastro-enteric wall have been the subject of an extended paper,[6] wherein it was shown that guinea-pigs can be sensitized through the medium of feeding.

Experimental Data.—In table 10 are listed the feeding experiments. Raw milk, smaco 303 and dried milks sensitized a large percentage

TABLE 10.—*Results of Feeding Experiments with Heated Milks*

	Number of Animals	Results of Sensitization		Sensitized, per Cent
		Positive	Negative	
Raw skimmed milk	63	33	30	52
Smaco 303	50	28	22	56
Dried milk	50	26	24	52
Boiled milk	66	18	48	27
Evaporated milk	85	21	64	25

TABLE 11.—*Results of Feeding Experiments with Evaporated Milk (80 Cc.)*

Number of Animal	Reaction to Shock Injections*		
	Bovine Serum, 1 Cc.	Lactalbumin, 0.011 Gm.	Casein, 0.028 Gm.
1	0	0	0
2	0	0	0
3	0	0	0
4	0	0	0
5	0	0	0
6	0	0	0
7	0	0	0
8	0	0	0
9	0	0	0
10	0	0	0
11	0	0	++
12	0	0	++
13	0	+	++++
14	0	+	++++
15	0	++++	
16	++++		

* The shock doses were administered intravenously.

TABLE 12.—*Results of Feeding Experiments with Acidified Milks*

	Number of Animals	Results of Sensitization		Sensitized, per Cent
		Positive	Negative	
Acidified raw milk	42	23	19	55
Acidified evaporated milk	44	5	39	11

(from 52 to 56 per cent) of the animals, whereas freshly boiled milk and evaporated milk sensitized to a much less degree (from 25 to 27 per cent).

Table 11 shows the results after the sensitizing dose of evaporated milk was fed and shock injections of bovine serum, lactalbumin and casein were given successively to the same animals. Two animals (11 and 12) manifested no reactions to bovine serum or lactalbumin

but reacted definitely to casein. In two other animals (13 and 14) there were no reactions to bovine serum, a moderate reaction to lactalbumin and a marked reaction to casein. This indicates that evaporated milk, when ingested, has largely lost the anaphylactogenic power of its globulin and lactalbumin fractions, but retains that of its casein fraction. At times, however, there is retained a sensitivity to the globulin and lactalbumin fractions, as was demonstrated in one of sixteen and one of fifteen animals, respectively.

In table 12 the influence of acidification on milk is shown. Acid added to raw milk does not change its anaphylactogenic properties, but when it is added to evaporated milk there is a greater reduction in antigenic properties than when plain evaporated milk is fed. This point is considered more fully later.

IDIOSYNCRASY TO MILK IN MAN [10]

Report of a Case.—During the course of these experiments we worked with a child who was exquisitely sensitive to milk. A boy, 9 years of age, had been sensitive since early infancy. He was breast fed for eighteen months, and when first given cow's milk manifested a severe allergic reaction, with vomiting and urticaria. The child was so sensitive that when milk was given subsequently he had severe attacks of asthma, even after taking a few drops. The physician who studied him several years previously attempted to build up a tolerance for milk by giving him doses of a drop at a time, yet when the child was finally given 1 teaspoonful of milk he had a severe asthmatic attack with cyanosis. When milk in any form entered his diet there developed a marked reaction. He came to our attention two years ago, and the parent was so insistent that milk was intoxicating that he did not permit us to make a clinical trial of even a drop. When the child was tested by the scratch method with milk proteins, he gave a moderate reaction to lactalbumin and to whole cow's milk. He was tested intracutaneously with the purified lactalbumin and casein (used in our animal experimentation) in doses of 0.02 cc. of a 1 per cent solution of lactalbumin and in a similar dose of 0.02 cc. of a 2.8 per cent solution of casein. There was no reaction to the casein, but within a few minutes after the test with lactalbumin there developed a severe asthmatic attack with marked cyanosis and moderate dilatation of the right side of the heart, and the child appeared to be going into anaphylactic shock. He was immediately given restorative measures by the administration of epinephrine and oxygen, but remained in shock for several hours. He was taken home, and the asthmatic phase continued for four days. The most interesting thing was that a moderate reaction to lactalbumin developed at the site of the test, but there was no reaction to casein. This patient was shown, therefore, to be exquisitely sensitive to lactalbumin and not to casein. There was no urticaria. From the symptoms, the shock organ in this case appeared to be the lungs.

We transferred the boy's serum to two guinea-pigs and obtained a definite passive sensitization to lactalbumin in one of the animals and a doubtful reaction in the other. Blood serum drawn during the severe attack was transferred to three guinea-pigs; the reaction to lactalbumin was negative in two and positive in the third.

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10. Idiosyncrasy to milk from the larger clinical aspect will be the subject of a subsequent paper.

The boy's blood serum was further transferred by the Prausnitz-Küstner method to the skin of normal children, and the presence of antibodies was demonstrated by positive cutaneous reactions. One child, who received no milk for forty-eight hours, was given a glass of milk to drink, and there resulted a strongly positive local cutaneous reaction twenty minutes after ingestion. These passive transfers all caused negative reactions to casein.

In attempting to give the patient milk, we started by giving 1 drop of raw milk diluted in one-half glass of water. This was gradually increased to several drops, when the child had an attack of asthma. We then resorted to evaporated milk and were able to give this until the child finally consumed a whole glass of evaporated milk diluted one half without untoward symptoms. The patient had such a fear of anything resembling milk that he had to be bribed to drink evaporated milk, even though we proved that it could be tolerated. The feeding was continued for weeks with absolute tolerance.

COMMENT

Wells and Osborne,[1] who were the first to study the anaphylactogenic properties of milk, using carefully prepared protein fractions, showed that casein, lactalbumin, lactoglobulin and an alcohol-soluble fraction from the casein were chemically distinct. Their work illustrated the dependence of immunologic specificity on chemical composition rather than on biologic origin and demonstrated that immunologic methods are a great aid and in many cases indispensable in preparing proteins in a state of purity. Grave doubt must be cast on most of the immunologic work done by the anaphylactic method with so-called pure proteins, because most investigators have used doses which were inadequate for the detection of impurities; they have failed to discover the sensitivity of the animals by a control shock dose of the original sensitizing substance, and they have utilized the unreliable intraperitoneal route for shock injections.

Reverting to table 1, it is shown that it is relatively difficult to sensitize to milk and that, therefore, large doses of milk must be used. Many investigators have used amounts entirely too small (from 0.2 to 1 cc.) for adequate sensitization or shock.

Tables 2 to 5 indicate definitely that casein, lactalbumin, lactoglobulin and bovine serum are highly anaphylactogenic to themselves and to raw milk. By employing chemically pure proteins and exacting immunologic methods it is shown that an almost complete separation of casein and lactalbumin can be obtained, though in rare instances an interrelation of the various isolated proteins is evident. Therefore, although our chemical separations were extensive, some crossing is still shown by the drastic tests that we have employed. This indicates how difficult it is to get an absolute separation of the proteins and how much contaminated the casein and whey fractions usually employed must be.

The pure proteins were utilized in the study of the changes that may or may not have taken place in heated milks. Evaporated milk and

smaco 303 (purported to be a hypo-allergic milk) were studied in greater detail than other modifications.

There are few studies on the immunologic properties of heated milks. Those of the early investigators, Moro, in 1901,[11] and Fuld, in 1902,[12] show that there was apparently no change in the antigenic properties of milk after being heated to 100 C. for one-half hour. In 1908, Wells [13] showed that the lack of change in heated milks was due to the fact that pure casein when heated to 100 C. for twenty-five minutes was not materially impaired in its antigenic activity. Kudicke and Sachs,[14] in 1914, and Versell,[15] in 1916, observed that antiserums obtained from boiled milk and its whey constituents are much less active than those from fresh milk. In 1928, von Baeyer [16] found similar changes to occur in goat's milk. The articles which bear particularly on the problem are those by Cutler,[17] in 1929, and Lewis and Hayden,[18] in 1932.

Cutler studied the antigenic properties of evaporated milk as compared with raw milk, employing the anaphylaxis, precipitin and complement-fixation methods. He concluded that there is a definite change in specificity of the whey proteins after evaporation and sterilization. His entire work must be criticized on the basis that he did not use purified proteins, but merely separations of casein and whey prepared by a single precipitation with acid. The number of animals used in arriving at the minimal lethal dose was so small as to preclude any possibility of establishing a quantitative relationship, and in the majority of instances the intraperitoneal route was used for shock injections. Cutler's precipitin tests were carried out with evaporated and raw milk as antigens, which have been found to be unsatisfactory because of their opalescent nature. The fact that he found a 50 per cent reduction of nitrogen in the whey fraction from evaporated milk as compared with that from raw milk warrants the conclusion that the antigens

11. Moro, E.: Biologische Beziehungen zwischen Milch und Serum, Wien. klin. Wchnschr. **14**:1073, 1901.

12. Fuld, E.: Ueber das Bordetsche Laktoserum, Beitr. z. chem. Phys. u. Path. **2**:425, 1902.

13. Wells, H. G.: Studies on the Chemistry of Anaphylaxis, J. Infect. Dis. **5**:449, 1908.

14. Kudicke, R., and Sachs, H.: Ueber das biologische Verhalten roher und gekochter Milch, Ztschr. f. Immunitätsforsch. **20**:316, 1914.

15. Versell, A.: Ueber das serologische Verhalten von Milch und Milcheiweisskörpern in frischem und gekochtem Zustand, Ztschr. f. Immunitätsforsch. u. exper. Therap. **24**:267, 1916.

16. von Baeyer, E.: Zur Kenntnis der Antigenfunktionen der Milch, Ztschr. f. Immunitätsforsch. u. exper. Therap. **56**:241, 1928.

17. Cutler, O. I.: Antigenic Properties of Evaporated Milk, J. A. M. A. **92**: 964 (March 23) 1929.

18. Lewis, J. H., and Hayden, H. C.: Effect of Heat on the Antigenic Properties of Milk, Am. J. Dis. Child. **44**:1211 (Dec.) 1932.

present in the whey of evaporated milk were reduced, but not necessarily changed, in specificity.

Lewis and Hayden undertook to ascertain and compare by means of the complement-fixation test the antigenic properties of raw and evaporated milk and smaco 303. They also used crude casein and acknowledged that in their preparations there were probably heat-coagulated proteins present to contaminate the caseins they obtained from evaporated milks and smaco. The filtrate, after the removal of the casein, was used for the whey proteins without further purification. They concluded that there is some decrease in antigenic properties of the whey proteins of evaporated milks and smaco 303 and that heating produced a change in the specificity. Because of the incomplete separation of the milk proteins, any conclusion with reference to specificity is unwarranted. They showed a definite decrease in the antigenic activity of the whey proteins when heated to 60 C., which became more marked when the temperature was increased. No change occurred in the casein until the temperature exceeded 110 C., when there was a marked decrease in the antigenic activity.

It is shown in our protocols that evaporated milk, smaco 303, milk freshly boiled for several hours, milks acidified with lactic acid and various dried milks can sensitize not only to themselves but to raw milk, purified casein and purified lactalbumin. There is a moderate diminution in the sensitizations to lactalbumin, while the sensitizing ability of the homologous globulin in bovine serum is largely lost after evaporation and boiling.

However, as a shock agent, there is a real and unmistakable loss of antigenic power of the whey proteins in evaporated milk and to a lesser degree in smaco 303 (tables 6 to 9). Several investigators [19] found as we did with milk that the sensitizing power of serum was retained but the intoxicating power lost when serum was heated to 90 C.

Casein itself has been known to be unaffected by heat, but it was thought that the lactalbumin and lactoglobulin fractions were chemically changed by heating. The fact that heated milks retain their ability to sensitize animals not only to purified casein but to purified lactalbumin

19. Besredka, A.: Du méchanisme de l'anaphylaxie vis-a-vis du sérum de cheval, Ann. Inst. Pasteur **22**:496, 1908. Rosenau, M. J., and Anderson, J. F.: Further Studies upon Anaphylaxis, United States Public Health Service, Hyg. Lab. Bull., 1908, no. 45. Doerr, R., and Russ, V. K.: Studien über Anaphylaxie, Ztschr. f. Immunitätsforsch. u. exper. Therap. **3**:706, 1909. Kraus, R., and Volk, R.: Zur Frage der Serumanaphylaxie, ibid. **1**:731, 1909; Weitere Beiträge zur Frage der Serumanaphylaxie, ibid. **3**:299, 1909. Uhlenhuth and Haendel: Untersuchungen über die praktische Verwertbarkeit der Anaphylaxie zur Erkennung und Unterscheidung verschiedener Eiweissarten, ibid. **4**:761, 1910. Wells.[13]

and raw milk indicates that no irreversible alteration of antigen or change in specificity takes place as a result of heating.

Exactly why the heating of milk causes a loss of its intoxicating power while it still retains its sensitizing ability, particularly to the lactalbumin, may have a twofold explanation: first, a part of the lactalbumin may escape coagulation, and, second, the denaturation may be reversed and the protein go into solution in the animal body to produce sensitization. With the intoxicating dose the small amount of uncoagulated lactalbumin is insufficient to produce shock except in rare instances and then to a slight degree. Resolution of the coagulum, on the other hand, may occur too slowly to furnish enough soluble antigen to produce shock.

Most of the work done on the denaturation of proteins by heat has been carried out with egg albumin and investigators have been unable to agree on a theory to explain the reaction of this particular protein under the influence of heat. Chick and Martin [20] have shown that the coagulation of protein by heat consists of two distinct processes: (1) denaturation, the alteration of the protein under the influence of heat, and (2) agglutination, the separation of the altered protein in a particulate form. Agglutination is now a fairly well understood phenomenon of colloidal chemistry, while the significance of denaturation is still obscure. We believe that the alteration of the whey protein is merely the result of the agglutination phase of coagulation by heat and not a true denaturation, which would indicate a changed specificity of the protein.

The feeding experiments with the various forms of milk were undertaken to determine whether there was a further diminution of sensitization when heated milks were fed. It was found that raw skimmed milk, smaco 303 and dried milks sensitized upward of 50 per cent of the animals, while milk freshly boiled for four hours showed a marked diminution in ability to produce sensitization, as did evaporated milk. This indicated that when milk is thoroughly heated to 100 C. or evaporated and sterilized at 116 C., there is a marked diminution in the ability to sensitize by mouth (table 10).

Table 11 shows how evaporated milk when fed almost entirely loses the power to sensitize to the whey proteins and, in a large measure, to the casein. The difference between feeding, therefore, and sensitization by injection of evaporated milk must be accounted for by another factor, namely, that the digestive enzymes more readily attack the proteins in heated milk and therefore impede their entrance through the normal gastro-enteric wall in an undigested state.

20. Chick, H., and Martin, C. J.: On the "Heat Coagulation" of Proteins, J. Physiol. **40**:404, 1910.

Mendel and Lewis [21] showed that in man raw egg white is digested only to a small extent and therefore is evacuated in an almost unchanged condition, whereas cooked egg white is digested to a greater degree. Bateman,[22] in 1916, showed that raw egg white is not digested in dogs, rats or rabbits, although egg white coagulated by boiling is readily digested. Hess, Koch and Sennewald [23] showed that boiling definitely facilitates the peptic digestion of milk, and Wallen-Lawrence and Koch [24] showed that raw milk, when pasteurized, boiled or evaporated, undergoes changes which make it more readily digested by trypsin in vitro than is raw milk. The changes are quantitatively greater for boiled and evaporated milk than for pasteurized milk.

Table 12 summarizes experiments to show the influence of acidification on the sensitizing quality of milks. It will be noted that acidification of raw milk does not alter its sensitizing ability when fed. However, when evaporated milk is acidified there is a notable decrease in the sensitizing ability. When acid is added to raw milk the soluble proteins in the separated whey largely escape digestion because of their fluid state, which permits rapid intestinal passage and entrance into the blood stream in a native state. With the evaporated milk the whey proteins are coagulated and the acid casein curd is extremely fine, so that all the proteins are more rapidly and completely digested.

When milk is evaporated, 50 per cent of the water is removed in vacuo, and the milk is then sealed in a can and sterilized for twenty minutes at 116 C. The removal of water before coagulation would prevent the proteins from redissolving to any large extent. This explanation, we believe, accounts largely for the greater loss of antigenic properties in evaporated milk and in milk freshly boiled for several hours.

Smaco 303, the so-called hypo-allergic fat-free milk, also showed a diminution in antigenic properties, but not to the same extent as evaporated milk. The exact details of the process of manufacture are not available, but the milk is not concentrated. It appears that it has been refluxed at the boiling temperature for several hours. We found that the whey derived from smaco 303 contained coagulable proteins, whereas the whey from evaporated milk showed an absence of these constituents.

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21. Mendel, L. B., and Lewis, R. C.: The Rate of Elimination of Nitrogen as Influenced by Diet Factors, J. Biol. Chem. **16**:19 and 37, 1913.

22. Bateman, W. G.: The Digestibility and Utilization of Egg Proteins, J. Biol. Chem. **26**:263, 1916.

23. Hess, J. H.; Koch, E. M., and Sennewald, Z. C.: Peptic Digestion of Cow's Milk, J. A. M. A. **87**:1360 (Oct. 23) 1926.

24. Wallen-Lawrence, Z., and Koch, F. C.: The Relative Digestibility of Unsweetend Evaporated Milk, Boiled Milk and Raw Milk by Trypsin in Vitro, Am. J. Dis. Child. **39**:18 (Jan.) 1930.

The absence of change in the antigenic properties of the dried milk must be explained on another basis. It was shown by Chick and Martin and others that crystalline egg albumin suffers no change by heating to 120 C. for five hours in a dry state and that methemoglobin was unaltered after four hours' heating to 110 C. According to their work the coagulation of protein is not a pure effect of temperature, for water, as such or in the form of steam, is essential. Proteins in a dry or nearly dry condition can therefore be heated to a much higher temperature without change than can proteins in the presence of water. The separation of water from the solid constituents in drying milk is almost instantaneous, therefore any further application of heat to the powdered milk does not cause change in its antigenic properties.

This subject would be of purely academic interest were the experimental evidence confined entirely to the animal, but its greatest interest lies in its relation to human idiosyncrasy to milk. It is generally believed that most persons with an intolerance for milk are sensitive to the whey proteins, which explains their tolerance for heated milks. In the case cited we have evidence that the child, 9 years of age, was exquisitely sensitive to lactalbumin but not to the casein fraction. The child was so intolerant as to exhibit severe forms of anaphylaxis after consuming an extremely small amount of milk, though when evaporated milk was given it was tolerated without any untoward effects, even in large amounts. So sensitive was the child that a minute injection of pure lactalbumin given intracutaneously induced an immediate anaphylactic reaction. His blood was shown to contain specific lactalbumin antibodies which could be passively transferred both to normal human skin and to guinea-pigs with subsequent anaphylactic reactions. It is apparent, therefore, that evaporated milk can be taken with impunity by persons markedly sensitive to the whey fractions of milk. If evaporated milk is acidified before using, the antigenic properties are further diminished, and it may be tolerated by the person sensitive to casein as well.

CONCLUSIONS AND SUMMARY

The proteins isolated from raw milk are chemically and biologically distinct.

There are no antigenic changes as a result of drying, acidification or pasteurization.

Dried, acidified, superheated or evaporated milk shows no loss of the antigenic properties of the casein fraction.

As a sensitizing agent given by injection milk which is evaporated, freshly boiled for several hours or superheated shows practically no loss of the antigenic character of the lactalbumin.

As a shock agent given by injection evaporated or superheated milk shows an unmistakable loss of the antigenic properties of the whey fraction. This is more marked with evaporated than with superheated milk (smaco 303).

Evaporated, freshly boiled and acidified evaporated milk, when fed by mouth, show a marked reduction in sensitizing ability.

The loss of the antigenic properties of heated milks is presumably due to coagulation of the whey proteins, for which there is some evidence of reversibility.

The further reduction in the antigenic properties of heated milks when fed by mouth is due to the fact that coagulation delays the passage of proteins through the gastro-intestinal tract, thus making for more complete digestion and diminishing the probability of the absorption of native antigens through the intestinal wall.

In view of our experimental and clinical observations, it appears that evaporated milk is the modification of greatest value for the person who is sensitive to milk.

ANAPHYLACTOGENIC PROPERTIES OF MALTED SUGARS AND CORN SYRUP

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It has generally been held that only such food substances as contain protein constituents are capable of producing those altered reactions in man which are grouped under the common term allergy. However, there has recently appeared a preparation of dextrimaltose sugar purported to be nonallergic, and the question has been raised as to whether food substances so widely used in infant feeding and ordinarily designated as being carbohydrates may give rise to exacerbations in the allergic person. The substances most commonly used in infant feeding are preparations of malt extracts, of dextrimaltose and of corn syrup. In this study we undertook to determine their anaphylactogenic properties.

EXPERIMENTAL DATA

Method.—The anaphylaxis method was used in these experiments. Normal guinea-pigs weighing from 250 to 350 Gm. were employed. All the animals were obtained from a reliable source and were raised on a known diet which did not contain barley, corn, wheat or milk. A negative reaction to the original sensitizing injection served as a control in each animal.

All solutions were made with distilled water. Except when specially noted, each animal was given a sensitizing injection of 5 cc. and a shock injection of 1 cc. The animals were uniformly sensitized by intraperitoneal injection and were given a shock injection approximately three weeks later by the intravenous route. All the preparations that were injected were sterilized by passage through a Seitz filter.

SERIES 1.—In this series of experiments it was sought to learn whether the original barley malt, malt extract and malt syrup, which constitute stages in the preparation of dextrimaltose, and dextrimaltose itself, which is a stage in the digestion process of these carbohydrates, are capable of acting as sensitizing agents.

A. Barley Malt.—Of nine animals sensitized with 5 cc. of a 5 per cent infusion of ground malt and given a shock injection of 1 cc. of

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the same infusion, four died of anaphylactic shock, one showed marked symptoms of shock but recovered, one showed moderate symptoms and three gave a negative reaction.

B. Malt Extracts.—Of the substances prepared from malt 5 cc. of a 10 per cent solution was used for sensitization and 1 cc. of the same solution was used for shock.

Preparation a (Brewers' Malt): Barley malt is cleaned by passing it through a series of machines which remove dust, chaff, clay, pebbles and other foreign materials. The malt is then ground in special mills, is weighed automatically and is dropped into mash tubs which are large tanks heated by steam coils and provided with stirrers and a filter bed bottom. A measured amount of heated potable water is then added to the malt, and the process of mashing is allowed to proceed. The temperature is adjusted to assure the optimum action of the malt enzymes in converting the starch into soluble carbohydrates and insoluble proteins. When tests show that the action of the enzymes has proceeded sufficiently, the material is filtered and pumped through sanitary pipes into vacuum evaporators, where it is concentrated to about 87 per cent solid matter (density, 42 degrees, Baumé). The average of many protein determinations on the barley malt extract show a content of about 5.5 per cent, using the standard protein factor N × 6.25. This malt extract is made exclusively from selected barley malt tested in the laboratory.

Result: Of ten animals, four died of anaphylactic shock, two manifested marked symptoms of shock but recovered and four gave a negative reaction.

Preparation b (Malt Extract, Plain): This is prepared in the manner described for brewers' malt, except that when the temperature reaches 150 F. the grain is converted into maltose and dextrin. Digestion of the albuminoids into soluble substances is caused by a peptase in the malted barley. This extract contains diastase, mineral salts, proteins, dextrin and maltose and has an acid reaction with a p_H of 5.4. The protein content (based on N × 6.25) is 4.4 per cent. About 10 per cent of glycerin is added as a preservative.

Result: Of seven animals, four died of anaphylaxis, two manifested symptoms of shock with recovery and one gave a negative reaction.

Preparation c (Malt Soup Extract): This is prepared in the same manner as is the plain malt extract except that the temperature is increased to 158 F. Potassium carbonate is added so that the final product is slightly alkaline and has an average p_H of 7.2. The finished product is heavier in density and is richer in mineral salts, dextrin and maltose than the preparation previously mentioned. The main difference, however, is in the p_H and in the diastatic activity. No glycerin is added. The protein content is 6.4 per cent.

Result: Of nine animals, five died of anaphylactic shock, two showed moderate symptoms of shock with recovery and two gave a negative reaction.

Preparation d (Malt Sugar): This is prepared from malted barley to which is added a special starch made from corn. The diastatic activity of the malted

barley is utilized to convert the starch into maltose. The p_H is controlled so that it averages 7.2. The final extract is concentrated to a syrup in vacuo, which is then dried in vacuum driers to a powder. The malt sugar differs from other preparations of dextrimaltose mainly in its richer content of maltose and its higher vitamin B potency. The main reason for not eliminating the proteins is that the vitamin B potency would be destroyed, as the preparation would have to be boiled, cooled and filtered. The protein content is 4.4 per cent.

Result: Of eleven animals, two died of anaphylactic shock, four showed marked symptoms of shock with recovery, two showed moderate symptoms of shock and three gave a negative reaction.

Preparation e (Malt Extract): This is an infusion, made by the method already described, which contains, in addition to ground malted barley, wheat and oats. After the desired consistency is obtained, 3.9 per cent ethyl alcohol is added for preservative purposes. The temperature employed is sufficiently low to have little destructive action on the enzymes and on vitamins B and G. The protein content is 4.9 per cent.

Result: Of thirteen animals, nine died of anaphylactic shock, one showed marked symptoms of shock with recovery, two showed moderate symptoms of shock and one gave a negative reaction.

Résumé.—Of fifty-nine animals used in the study of barley malt and malt extracts, forty-five animals manifested varying degrees of anaphylactic shock, twenty-eight of which died of anaphylactic shock while seventeen showed symptoms of shock with recovery. From these figures we conclude that these substances are highly anaphylactogenic and are capable of rendering animals hypersensitive.

C. Preparations of Dextrimaltose.—Dextrimaltose can be made from any form of starch by treating boiled starch with an infusion of barley malt.

Preparation a: A cereal starch from corn having a low fat content is mixed with water and cooked in a closed retort by the injection of live steam. A malt high in diastase is then added and the complete conversion of starch into maltose and dextrins is effected during the remainder of the cooking period. Careful control and numerous tests to determine the percentage of these materials is necessary before all traces of starch can be eliminated. The mixture is then brought to a boil and filtered. After cooling a further purification is effected by running the product through high speed clarifiers; it is decolorized by being filtered through sterile animal charcoal, concentrated to a thick syrup and dried in vacuum drum driers. Before drying the p_H of the syrup is adjusted to neutrality.

The proteins of the corn starch and the soluble proteins of the malt either are insoluble or become insoluble on boiling, so that ordinary filtration suffices for their removal. The additional filtration with animal charcoal adsorbs a further amount of nitrogenous material. The finished product contained 0.2 per cent of protein.

Result: With a 5 per cent solution, ten animals gave a negative reaction, as did ten animals with a 10 per cent solution. With a 20 per

cent solution nine animals gave a negative reaction. Of seven animals each of which was given three sensitizing injections and a shock injection of the 20 per cent solution all gave a negative reaction.

Preparation b: This is dextrimaltose prepared as just described, but made from potato starch.

Result: A 10 per cent solution was used. Of ten animals, all gave a negative reaction.

Preparation c: This is dextrimaltose made from potato starch but not filtered through bone black.

Result: A 10 per cent solution was used. Of eight animals, all gave a negative reaction.

Preparation d: This is dextrimaltose made from corn-starch but not filtered through bone black.

Result: A 10 per cent solution was used. Of ten animals, all gave a negative reaction.

Preparation e: Dextrimaltose made from potato flour which is purported to be hypo-allergic is prepared by a special process in which the mix is autolyzed so that the finished product does not give the usual reactions for protein.

Result: With a 10 per cent solution, all of nine animals gave a negative reaction. Of six animals sensitized with three injections of a 20 per cent solution, all gave a negative reaction.

Résumé.—Of seventy-nine animals used in the study of reactions to the combination of carbohydrates commercially known as dextrimaltose, all gave a negative reaction showing that dextrimaltose, irrespective of the type of starch used and of certain details in the process of manufacture, is nonanaphylactogenic. The original substances appear to lose their antigenic properties in the process of the manufacture of the various preparations of dextrimaltose.

D. Corn Syrup.—Corn-starch is suspended in water and heated in an autoclave by steam in the presence of a small amount of a catalyst (pure hydrochloric acid). Hydrolysis ensues, and the resulting solution is free from starch when removed from the converter. The carbohydrates are present as reducing sugars, dextrose and some maltose and dextrin. There is about 0.2 per cent of protein. At the end of the conversion the acid solution is neutralized to the proper p_H value. The precipitate formed at this point is removed by mechanical filtration. A series of filtrations through animal charcoal follows for purification and decolorization. The concentration is stopped at the proper specific gravity for this syrup.

Result: Of eleven animals sensitized with syrup used in the preparation of dextrimaltose, containing 2.7 per cent of corn protein, all gave a negative reaction. Of eight animals sensitized with a standard preparation of corn syrup all gave a negative reaction.

Résumé.—Corn syrup, both the ordinary commercial product and the particular malted syrup used in the preparation of certain kinds of dextrimaltose, is nonanaphylactogenic.

SERIES 2.—In this series of experiments an attempt was made to determine whether a cross-relationship could be elicited between the original substances which possess antigenic properties and the finished product, dextrimaltose.

A[1]. *Sensitization with Dextrimaltose; Shock with Malt Extract.*—Of three animals sensitized with 5 cc. of a 5 per cent solution of dextrimaltose and given a shock injection of 1 cc. of a 5 per cent solution of malt extract, all gave a negative reaction. Of ten animals sensitized with 5 cc. of a 10 per cent solution of dextrimaltose and given a shock injection of 1 cc. of a 10 per cent solution of malt extract, all gave a negative reaction. Of eight animals sensitized with three injections of 5 cc. of a 20 per cent solution of dextrimaltose and given a shock injection of 1 cc. of a 10 per cent solution of malt extract, all gave a negative reaction.

B[1]. *Sensitization with Malt Extract; Shock with Dextrimaltose.*—Of twenty animals sensitized with 5 cc. of a 10 per cent solution of malt extract and given a shock injection of 1 cc. of a 10 per cent solution of dextrimaltose, all gave a negative reaction. Seventeen of the animals received a second shock injection of 1 cc. of malt extract one hour after the shock injection of dextrimaltose was given; all gave an anaphylactic reaction. The positive reaction to the second shock injection of malt extract showed that the animals were properly sensitized and validated the negative reaction obtained with the dextrimaltose. An absence of any immunologic reaction between the malt extract and its simpler carbohydrate, dextrimaltose, indicated that there was no conjugated carbohydrate-protein present.[1]

C[1]. *Sensitization with Corn Syrup; Shock with Dextrimaltose.*—Of three animals sensitized with a standard brand of corn syrup and given a shock injection of dextrimaltose, all gave a negative reaction.

D[1]. *Sensitization with Dextrimaltose; Shock with Corn Syrup.*—Of ten animals sensitized with dextrimaltose and given a shock injection of standard corn syrup, all gave a negative reaction.

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1. (*a*) Goebel, W. F., and Avery, O. T.: Chemo-Immunological Studies on Conjugated Carbohydrate-Proteins: I. Synthesis of *p*-Aminophenol β-Glucoside, *p*-Aminophenol β-Galactoside, and Their Coupling with Serum Globulin, J. Exper. Med. **50**:521, 1929. (*b*) Avery, O. T., and Goebel, W. F.: Chemo-Immunological Studies on Conjugated Carbohydrate-Proteins: II. Immunological Specificity of Synthetic Sugar-Protein, ibid. **50**:533, 1929.

Résumé.—It was not possible to induce shock with dextrimaltose in animals that had been sensitized with malt extract; conversely, it was not possible to induce shock with antigenic malt extract in animals which had been sensitized with dextrimaltose. All the animals in this group that were sensitized with malt extract and that showed no reaction when given an injection of dextrimaltose after an incubation period, subsequently (that is, one hour later) gave a positive reaction when given an injection of malt extract. This demonstrates that the animals were specifically sensitized to malt extract and further bore out the conclusion that in the process of the manufacture of dextrimaltose the malt extract loses its anaphylactogenic properties. There was no cross-antigenic relationship found between dextrimaltose and corn syrup.

SERIES 3.—The materials used in this series were in the main derived from barley and corn. To further the search for the source of the anaphylactogenic properties of the malt preparations and to determine whether some small amount of antigenic proteins was present in the dextrimaltose preparations that were not demonstrable by the experiments already described, additional experiments were carried on in which purified proteins, hordein from barley and zein from corn, were used. These were prepared for us by Prof. R. Keith Cannan of the chemistry department. Each was used in a 20 per cent solution of alcohol.

A^2. Sensitization with 5 Cc. of a 5 Per Cent Infusion of Ground Malt; Shock with a 0.5 Cc. Alcoholic Solution of Hordein.—Of three animals, two died of typical anaphylactic shock and one gave a negative reaction.

B^2. Sensitization with 5 Cc. of a 10 Per Cent Solution of Brewers' Malt; Shock with 1 Cc. of Hordein.—Of eight animals, three died of anaphylactic shock and five gave a negative reaction. In one animal an experiment with a Dale uterine strip was performed; a positive result was obtained and was confirmed by subsequent intravenous injection (figure).

C^2. Sensitization with 5 Cc. of a 10 Per Cent Solution of Malt Sugar; Shock with 0.5 Cc. of Hordein.—Of three animals, two died of anaphylactic shock, and one showed symptoms of shock with recovery.

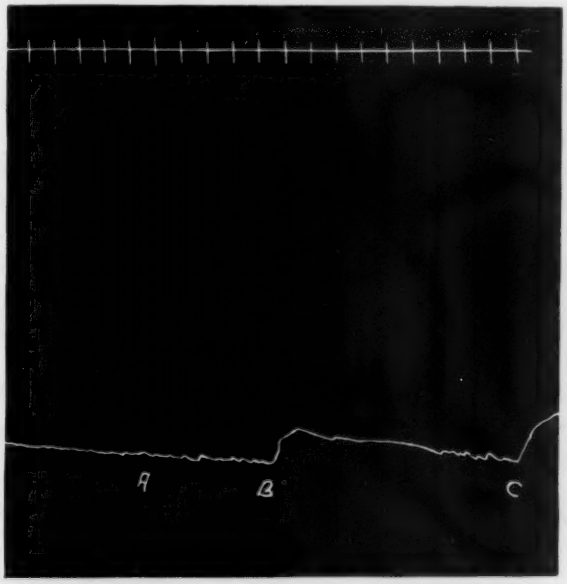
D^2. Sensitization with 5 Cc. of a 10 Per Cent Solution of Dextrimaltose; Shock with 1 Cc. of Hordein.—The six animals used in this experiment gave a negative reaction.

E^2. Sensitization with 5 Cc. of a 10 Per Cent Solution of Malt Sugar; Shock with 0.5 Cc. of Zein.—The six animals used gave a negative reaction.

F[2]. *Sensitization with 5 Cc. of a 10 Per Cent Solution of Dextrimaltose; Shock with 0.5 Cc. of Zein.*—The six animals used gave a negative reaction.

Résumé.—The antigenic nature of barley malt, malt extract and malt sugar is shown to be related to the constitutent of barley protein, hordein. There was no cross-antigenic relationship between dextrimaltose and hordein. Apparently no anaphylactogenic relationship is present between malt sugar and zein or between dextrimaltose and zein.

SERIES 4.—Since certain preparations of dextrimaltose are available which contain extraneous substances, we sought to determine



A guinea-pig was sensitized with 5 cc. of a 10 per cent solution of brewers' malt extract injected intraperitoneally. Two weeks later the animal was anesthetized and the uterine horn was removed for the Schultz-Dale test. After the animal had completely recovered from the effects of the anesthesia it was given intravenously a shock injection of 1 cc. of hordein (Ratner, Bret, and Gruehl, H. L.: Comparison of Methods Used in the Study of Anaphylaxis, *J. Lab. & Clin. Med.* **16**:1069, 1931). The animal died of typical anaphylactic shock.

A indicates the lack of reaction when 1 cc. of dextrimaltose was injected; *B*, the positive response to 1 cc. of hordein, and *C*, the nonspecific muscle contraction with 0.003 Gm. of histamine.

whether the added substances produced antigenic changes. Preparation X is a preparation of dextrimaltose to which is added a vitamin B complex derived from brewers' yeast and wheat embryo (4.3 per cent of protein). Preparation Y is a preparation of dextrimaltose to

which wheat embryo has been added (8 per cent of protein). Preparation Z is a preparation of dextrimaltose which contains 69 per cent of carbohydrates in the form of lactose, maltose and dextrin to which is added dried homogenized cow's milk (5.5 per cent of protein).

A[3]. *Sensitization with a 10 Per Cent Solution of Preparation X; Shock with a 10 Per Cent Infusion of Wheat Germ.*—Of five animals, three showed marked symptoms of anaphylactic shock with recovery and two gave a negative reaction.

B[3]. *Sensitization with a 10 Per Cent Solution of Preparation Y; Shock with (1) a 10 Per Cent Infusion of Wheat Germ and (2) a 10 Per Cent Solution of Preparation Y.*—1. Of three animals, two showed marked symptoms of shock with recovery and one, moderate symptoms of shock.

2. Of two animals, one showed marked symptoms of shock with recovery and one gave a negative reaction.

C[3]. *Sensitization with Raw Milk; Shock with a 10 Per Cent Solution of Preparation Z.*—Of four animals, two died of anaphylactic shock, one manifested marked symptoms of shock with recovery and one gave a negative reaction.

Résumé.—When extraneous substances, such as wheat germ or dried milk, were added to preparations of nonanaphylactogenic dextrimaltose, the antigenic properties resident in the new products were shown to be due to the added protein.

The complete findings showing how the malted sugars and corn syrups studied differ with reference to antigenic content are summarized in the following table.

Anaphylactogenic Properties of Malted Sugars and Corn Syrups

Preparation	Protein (N × 6.25), Percentage	Anaphyloctogenic Property	Anaphylactogenic Protein Constituents
Dextrimaltose sugars made from corn..	0.2	Absent	
Dextrimaltose sugars made from potato	0.2	Absent	
Corn syrups	0.2	Absent	
Brewers' malt extract	5.5	Present	Barley
Malt syrups	4.4 to 6.4	Present	Barley
Malt sugars	4.4	Present	Barley
Dextrimaltose containing vitamin B with wheat germ added	4.3 to 8	Present	Wheat
Dextrimaltose sugar with powdered milk added	5.5	Present	Milk

COMMENT

The experiments reported in this paper showed that malt extracts are anaphylactogenic and that this property depends on the protein constituents of the barley malt used in their preparation. Whether these malt preparations are plain or alkalinized or are in the form of

syrup or dried, they are antigenic. In the preparation of malt extracts very little heat is used in order to permit the optimum action of the malt enzymes. After filtration the syrup is concentrated in vacuum evaporators, and approximately 5 per cent of protein remains.

Corn syrups are nonanaphylactogenic, because the corn-starch is heated in an autoclave in the presence of pure hydrochloric acid, which results in complete hydrolysis. The precipitate formed is removed by mechanical filtration. The protein content of the final product is 0.2 per cent.

Hordein, a protein derived from barley, was shown to be responsible for the antigenic properties of the barley malt, the malt extracts and the malt sugar. Zein, a protein derived from corn, plays no rôle in the anaphylactogenic character of the malt sugars derived from corn. It is therefore assumed that the antigenic specificity of the malt extracts and malt sugars is dependent in part if not entirely on the barley proteins present in these preparations.

The so-called dextrimaltose sugars, whether made from corn-starch or from potato starch and prepared by special methods of superheating or without the final filtration through bone black, were shown to be notably devoid of anaphylactogenic properties. In the preparation of these sugars the malt extract is boiled and filtered several times, after which the syrup is reduced to a dry state in vacuum driers. Thus most of the soluble proteins present in the malt extract are rendered insoluble by boiling and are then filtered off. The final product contains approximately 0.2 per cent of protein. The soluble proteins of the corn-starch or potato flour used in these preparations of dextrimaltose become insoluble in the process of cooking. Although dextrimaltose contains 0.2 per cent of protein (based on the standard protein factor $N \times 6.25$), the absence of immunologic reactions to it may be due to the fact that the nitrogen which remains after the proteins have been coagulated and removed by filtration represents nonprotein nitrogen or denatured protein. The filtration through animal charcoal may cause adsorption of some of the impurities and decolorize the final product, but, as has been shown in these experiments, this step plays no rôle in any further reduction of the antigenic potency.

The possible relation that the carbohydrate itself plays in antigenic specificity was suggested by the work of Dochez and Avery,[2] who observed that filtrates of cultures of pneumococcus contained a stable substance which reacted specifically to antipneumococcus serum of the homologous type. This observation led to the isolation and identification of these specifically reacting substances from the three

2. Dochez, A. R., and Avery, O. T.: The Elaboration of Specific Soluble Substance by Pneumococcus During Growth, J. Exper. Med. **26**:477, 1917.

specific types of Pneumococcus [3] and from the three types of the Friedländer bacillus.[4] Since then other investigators have isolated similar substances from various other species of bacteria.[5] These type-specific substances fall into the class of carbohydrates. Immunologically they belong to that important group of specifically reactive but nonantigenic substances which Landsteiner termed haptens.

For the purpose of studying the rôle which simple sugars of different spatial configuration play in altering the specificity of proteins, Goebel and Avery [1a] synthesized dextrose and galactose hexosides to serum globulin and crystalline egg white. Avery and his co-workers [6] showed that the immunologic specificity of the conjugated carbohydrate-proteins depends on the carbohydrate.

In our experiments no reaction occurred when animals were sensitized with malt extract and were given a shock injection of dextrimaltose. Apparently a carbohydrate-protein relationship was not present. The antigenic specificity of the barley protein, we believe, is the explanation of the results we obtained.

The addition of elements such as wheat germ or dried milk to non-anaphylactogenic preparations of dextrimaltose converts them into substances which are definitely anaphylactogenic. Honey has long been accepted as a notable cause of allergic symptoms. Cases of sensitivity to honey have been described by Rowe,[7] and in 1909 Smith [8]

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3. Heidelberger, M., and Avery, O. T.: The Soluble Specific Substance of Pneumococcus, J. Exper. Med. **38**:73, 1923; **40**:301, 1924. Goebel, W. T.: ibid. **42**:727, 1925. Zinsser, H., and Parker, J. T.: Further Studies on Bacterial Hypersusceptibility, ibid. **37**:275, 1923.

4. Heidelberger, M.; Goebel, W. F., and Avery, O. T.: The Soluble Specific Substance of a Strain of Friedländer's Bacillus, J. Exper. Med. **42**:701, 1925. Goebel, W. F., and Avery, O. T.: Soluble Specific Substance of Friedländer's Bacillus; Isolation and Properties of Specific Carbohydrates from Types A and C, Friedländer's Bacillus, ibid. **46**:601, 1927.

5. (*a*) Mueller, J. H., and Tomcsik, J.: The Chemical Nature of Residue Antigen Prepared from Yeast, J. Exper. Med. **40**:343, 1924. (*b*) Laidlaw, J. P., and Dudley, H. W.: A Specific Precipitating Substance from Tubercle Bacilli, Brit. J. Exper. Path. **6**:197, 1925. (*c*) Mueller, J. H.; Smith, D., and Litarozek, S.: "Residue Antigen" from a Strain of Friedländer Bacillus, Proc. Soc. Exper. Biol. & Med. **22**:373, 1925. (*d*) Hitchcock, G. H.: Serological Relationships Among and Between Streptococci and Pneumococci, J. Exper. Med. **41**:13, 1925. (*e*) Lancefield, R. C.: The Immunological Relationships of Streptococcus Viridans and Certain of Its Chemical Fractions, J. Exper. Med. **42**:377, 1925.

6. Tillett, W. S.; Avery, O. T., and Goebel, W. F.: Chemo-Immunological Studies on Conjugated Carbohydrate-Proteins; Active and Passive Anaphylaxis with Synthetic Sugar-Proteins, J. Exper. Med. **50**:551, 1929. Laidlaw and Dudley.[5b]

7. Rowe, Albert H.: Food Allergy, Philadelphia, Lea & Febiger, 1931.

8. Smith, H. C.: Buckwheat Poisoning, Arch. Int. Med. **3**:350 (May) 1909.

reported that a patient sensitive to buckwheat could not tolerate buckwheat honey but could tolerate other types. The flavor, color and density of honey vary with the flower which is the source of the nectar. It is possible, therefore, that the sensitivity to honey may be due to the specific protein constituents of the source of the nectar.

During the course of this study we observed the case of a boy of 12 years who gave a positive intracutaneous reaction to barley and malt extract but a negative reaction to dextrimaltose. The boy, who was asthmatic, had a severe attack of asthma which was precipitated by drinking a malted brew. We have had a number of patients sensitive to wheat who after all other foods containing wheat were eliminated from the diet had exacerbations that were finally traced to preparations of dextrimaltose containing vitamin B obtained from wheat germ. It becomes obvious, therefore, that in the treatment of a patient who is hypersensitive to food the elimination of offending factors may be more complicated than is apparent when one considers that a protein may insidiously enter the diet as a constituent of a carbohydrate food.

CONCLUSIONS

Malt extracts and the barley malt from which they are derived are highly anaphylactogenic and react specifically to the original protein constitutent, hordein, present in barley. Persons who are sensitive to barley may show allergic symptoms after the ingestion of malt extracts and malt brews.

Corn syrups are nonanaphylactogenic.

Pure dextrimaltose sugars are nonanaphylactogenic.

It is improbable that any of the highly purified and refined sugars have anaphylactogenic properties.

The addition of wheat germ or dried milk to nonanaphylactogenic preparations of dextrimaltose converts them into substances which are definitely anaphylactogenic. Persons sensitive to wheat, yeast or milk may have allergic exacerbations from the use of such compound preparations of dextrimaltose.

Those who cannot tolerate honey may be sensitive to the specific protein elements of the nectar from which it is derived, for example, buckwheat.

Allergy to carbohydrate foods cannot therefore be attributed to the carbohydrates per se but must be ascribed to the protein constitutents which are added to certain compound carbohydrate food preparations.

The experiments reported make it apparent that pure dextrimaltose, corn syrup and crystalline sugars play no rôle in allergy.

BLOOD PHOSPHORUS DURING DEVELOPMENT AND HEALING OF RICKETS

NOTES ON THE LACK OF RELATIONSHIP BETWEEN THE LEVEL OF PLASMA PHOSPHORUS AND THE RACHITIC STATE

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CINCINNATI

For many years after Iverson and Lenstrup [1] and Howland and Kramer [2] found low values for inorganic serum in rachitic children, this change in blood chemistry was regarded not only as a constant symptom but also as an etiologic factor in active rickets. However, in the last few years several investigators have concluded that certain clinical as well as experimental observations indicate a lack of relationship between the development and cure of rickets and the concentration of inorganic phosphorus in the blood. In 1922 Hess and Unger [3] stated that normal values for inorganic blood phosphorus are occasionally found in rickets. In an experimental study in rats, Hess, Weinstock, Rivkin and Gross [4] pointed out:

> Rickets may be associated with normal concentrations of inorganic phosphorus in the blood. If milk is incorporated in a standard rickets-producing ration and small amounts of irradiated ergosterol are added, the inorganic phosphorus is raised to the normal level without accompanying signs of healing of the rachitic lesion. Animals which receive supplements of cod liver oil do not attain as high a concentration of phosphorus but do show definite evidences of healing.

Marfan [5] contended that hypophosphatemia is not a regular symptom of rickets and does not parallel the severity of the disease. He is of the opinion that hypophosphatemia can by no means be considered to be the cause of rickets. Stearns and Boyd [6] reported roentgenologic evidence of the healing of rickets coincident with a persistently low inorganic phosphorus content of the serum in two children.

From The Children's Hospital Research Foundation and the Department of Pediatrics, College of Medicine, University of Cincinnati.

1. Iverson and Lenstrup: Hospitalstid. **62**:1079, 1919.
2. Howland, J. F., and Kramer, B.: Calcium and Phosphorus in Serum in Relation to Rickets, Am. J. Dis. Child. **22**:105 (Aug.) 1921.
3. Hess, A. F., and Unger, L. J.: Infantile Rickets; Significance of Clinical, Radiographic and Chemical Examinations in Its Diagnosis and Incidence, Am. J. Dis. Child. **24**:327 (Oct.) 1922.
4. Hess, R. F., and others: J. Biol. Chem. **87**:37, 1930.
5. Marfan, A. B.: Presse méd. **40**:561 (April 13) 1932.
6. Stearns, M. J., and Boyd, J. D.: J. Clin. Investigation **10**:591 (Aug.) 1931.

On the other hand, instances of normal values for blood phosphorus in children with active rickets in whom there were no signs of healing have come under my observation. I attempted to explain these cases by assuming that the children had increased their stores of vitamin D by a brief exposure to the sun or by a temporary change in their diet. Thus an insufficient amount of vitamin D might be thought to cause a transitory increase of the inorganic serum phosphorus without curing the rickets clinically. On the contrary, in rachitic rats that had received a relatively large single dose of viosterol, I found low inorganic phosphorus values (from 2 to 3 mg. per hundred cubic centimeters) in the blood after from three to four days, although roentgenologically the animals showed complete healing of the rickets after ten days.

Certain questions presented themselves. Is there a rapid increase of the inorganic blood phosphorus in a rachitic organism after the administration of a single large dose of viosterol, and does the phosphorus return again to the low values if the rickets-producing diet is continued? Or is the increase gradual, as has been observed after the daily administration of small therapeutic doses of viosterol (Kramer, Shear and Siegel [7])?

These questions cannot be decided by experimentation on children, because children should not be subjected to a diet deficient in phosphorus and vitamin D. The experiments were therefore made on rats, by the use of a method that permits the estimation of inorganic blood phosphorus in small amounts of blood. In 1927 I [8] modified the Bell-Doisy method for the determination of the inorganic phosphorus in the blood in such a way that the amount of serum or plasma required was reduced from 2 to 0.2 cc. This modification has been successfully used for clinical purposes by many investigators (Wiskott, Freudenberg, von Rose and Bahl).[9] However, for certain experiments 0.2 cc. of blood is still too much, especially in animals as small as rats. It has therefore seemed worth while to attempt a further reduction in the amount of blood necessary.

METHODS

The method of colorimetric determination of phosphorus, as recommended by Kuttner and his co-workers,[10] appeared to be suitable, since the color developed by the reduction with stannous chloride is approximately four times as intensive as that obtained by the usual methods. Thus a fourth of the amount of blood used in my original modification, or 0.05 cc. of serum or plasma, was employed, and

7. Kramer, B.; Shear, M. B., and Siegel, J.: J. Biol. Chem. **91**:271 (April) 1931.

8. Warkany, J.: Biochem. Ztschr. **190**:336, 1927.

9. Wiskott, A.: Ztschr. f. Kinderh. **49**:79, 1930. Freudenberg, E.: ibid. **51**: 267, 1931. von Rose, Margarethe: ibid **54**:236, 1933. Bahl, E.: ibid. **46**:563, 1928.

10. Kuttner, T. T., and Cohen, H. R.: J. Biol. Chem. **75**:517 (Nov.) 1927. Kuttner, T. T., and Lichtenstein, L.: ibid. **86**:671, 1930.

results were obtained that agreed with those of the methods generally used. The reaction, however, is sensitive, and even slight contamination or an apparently unimportant change may cause a disturbance. Furthermore, in the modification that I have used the color does not obey Beer's law. In spite of these difficulties it has been possible to construct an empirical curve that gives the corresponding phosphorus value for a certain reading.

The required amount of serum or plasma (0.1 cc. for duplicate determinations) can easily be obtained from the jugular, femoral or brachial vein in rats, and from four to six determinations have been made on one rat.

The following reagents are used:

1. Three and five-tenths per cent trichloracetic acid.
2. One part ten normal sulphuric acid and 2 parts distilled water.
3. Freshly prepared 7.5 per cent sodium molybdate in distilled water.
4. Forty per cent stannous chloride in concentrated hydrochloric acid.
5. Standard stock solution: 0.3509 Gm. mono-potassium phosphate (Merck: Sørensen salt) in 1,000 cc. of water.
6. Standard 1: 2.5 cc. of standard stock solution and 7.5 cc. of water made up to 200 cc. with 3.5 per cent trichloracetic acid.
7. Standard 2: 5 cc. of standard stock solution and 5 cc. of water made up to 200 cc. with 3.5 per cent trichloracetic acid.
8. Standard 3: 10 cc. of standard stock solution made up to 200 cc. with 3.5 per cent trichloracetic acid.

All of the reagents are recommended by Kuttner and Cohen and Kuttner and Lichtenstein,[10] with the exception of the trichloracetic acid and the standard solutions.

Five-hundredths cubic centimeter of plasma is drawn into a special fine bore pipet (the distance between the mark and the point is 10 cm.). The plasma is then blown into a tube of a capacity of about 2 cc., and the pipet is rinsed with 0.05 cc. of distilled water, which is added to the measured serum. Nine-tenths cubic centimeter of 3.5 per cent trichloracetic acid is then added to precipitate the protein. The total volume is 1 cc. The precipitate is allowed to stand for ten minutes, after which it is filtered through a Pregl filter containing a layer of from 1 to 2 mm. of asbestos. Usually filtration takes place without difficulty, but if the process is too slow it can be accelerated by the method described in an earlier paper.[8] Five-tenths cubic centimeter of the filtrate is pipetted into a 1 cc. graduated flask, and 5 cc. of one of the standard solutions (1, 2 or 3) is put into a 10 cc. graduated flask.

The final reagents, which should be prepared just before the color is developed, are made according to the directions given by Kuttner and Cohen and Kuttner and Lichtenstein.[10] Eighteen cubic centimeters of sulphuric acid (reagent 2) is poured into 6 cc. of the sodium molybdate solution (reagent 3). This mixture should be colorless. If it appears green, it should not be used. In another test tube 0.1 cc. of the stannous chloride solution (reagent 4) is diluted with 20 cc. of distilled water. To develop the color, 4 cc. of the sulphuric acid-sodium molybdate mixture is pipetted into the 10 cc. flask containing 5 cc. of the standard solution, and 0.4 cc. into the 1 cc. flask containing 0.5 cc. of filtrate. Then 1 cc. and 0.1 cc. of the diluted stannous chloride reagent are allowed to flow along the walls of the 10 cc. and the 1 cc. flask, respectively. To obtain good results, the stannous chloride should be allowed to flow in slowly and form a layer of cloudy blue color

in the neck of the flask. Then the solutions are mixed by bubbling air through them by means of a glass capillary, and a clear blue color is obtained.

After from three to five minutes the solutions are compared in a micro-Dubosq colorimeter. A small portion of the standard solution is poured into one cup, and the contents of the 1 cc. flask into the other. The colorimeter is set at 20 mm. on the side of the standard, and the other side is adjusted until the color in both tubes is alike. The corresponding values for phosphorus in milligrams per hundred cubic centimeters in plasma and serum are read from a curve (chart 1). Readings between 11.8 and 33.6 can be used. The standard, however, should be chosen in such a way that its color and that of the sample are as nearly alike as possible; that is, the reading should be around 20. For my purposes the three standard solutions mentioned were sufficient, and values from 1 to 16 mg. can be read from the curve.

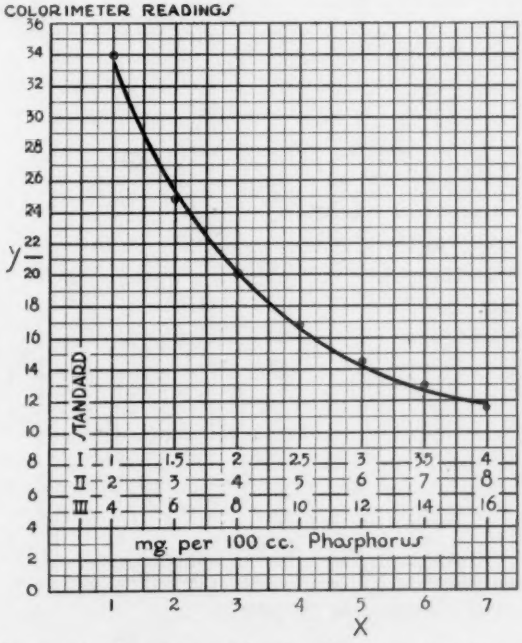

Chart 1.—Curve showing the relationship between the observed colorimetric readings and the serum phosphorus in milligrams per hundred cubic centimeters. Dr. Thomas J. LeBlanc (Department of Preventive Medicine, Medical College, University of Cincinnati) constructed the curve. The observed points were fitted with an exponential type curve of the type $y = K + 10^{a+bx}$ in which the lower asymptote was at the level 10, y was the reading in the colorimeter with standard at 20 and x was an arbitrary spacing on the X axis, which shows milligrams of phosphorus per hundred cubic centimeters. The fitted curve is expressed by the following:

$$y = 10 + 10^{1.56001 - 0.18667x}$$

Observed y	x	Calculated y	Deviations
34.0	1	33.6	+0.4
24.7	2	25.4	—0.7
20.0	3	20.0	0
16.7	4	16.5	+0.2
14.5	5	14.2	+0.3
12.9	6	12.8	+0.1
11.6	7	11.8	—0.2

EXPERIMENTS

Effect of Single Doses of Vitamin D on Rachitic Rats.—Rats weighing 50 Gm. were put on the Steenbock and Black diet no. 2,965 for three weeks. After this time, if there was roentgenologic evidence of the presence of rickets, the inorganic phosphorus of the (oxalate) plasma was determined. Two series of experiments were carried out. In the first series, after the administration of 10 drops of viosterol (250 D), determinations of phosphorus were made on different days (from two to four determinations in the same animal) without regard for the influence of the loss of blood on the values. In the second series, in order to avoid the possible influence of repeated bleeding at such short inter-

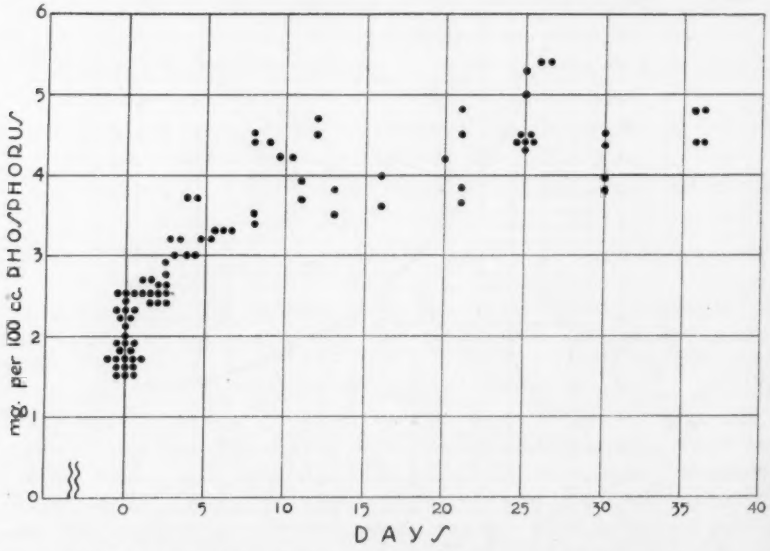

Chart 2.—Representation of the increase of inorganic phosphorus in rats after the administration of a single dose of viosterol.

vals, a week was allowed to elapse after the preliminary determinations. Then from 2 to 5 drops of viosterol (250 D) was given, and one additional determination was made on different days, each rat being bled only once. In both series roentgen examinations made on the tenth day showed almost complete healing. The determinations of phosphorus in both series were continued beyond the ten day period. The diet was not changed during the experiments. Since the animals showed the same reaction in both series, the values were combined in chart 2.

After the rats had received a rickets-producing diet for three weeks, the average value for phosphorus was 2 mg., with variations ranging from 1.5 to 2.6 mg. Viosterol was then given, and within twenty-four hours the phosphorus values had increased. After 10 days, at which

time there was roentgenologic evidence of healing of the rickets, values of about 4 mg. were reached. These represent an increase of approximately 100 per cent as compared with the results first obtained but are still much lower than the normal value (7.6) obtained in rats fed a standard diet (Bill's modification of Steenbock's stock ration). After the ten day period of healing a slow increase in the phosphorus was observed, although the animals were still fed the diet low in phosphorus. As late as five weeks after the administration of a single dose of vitamin

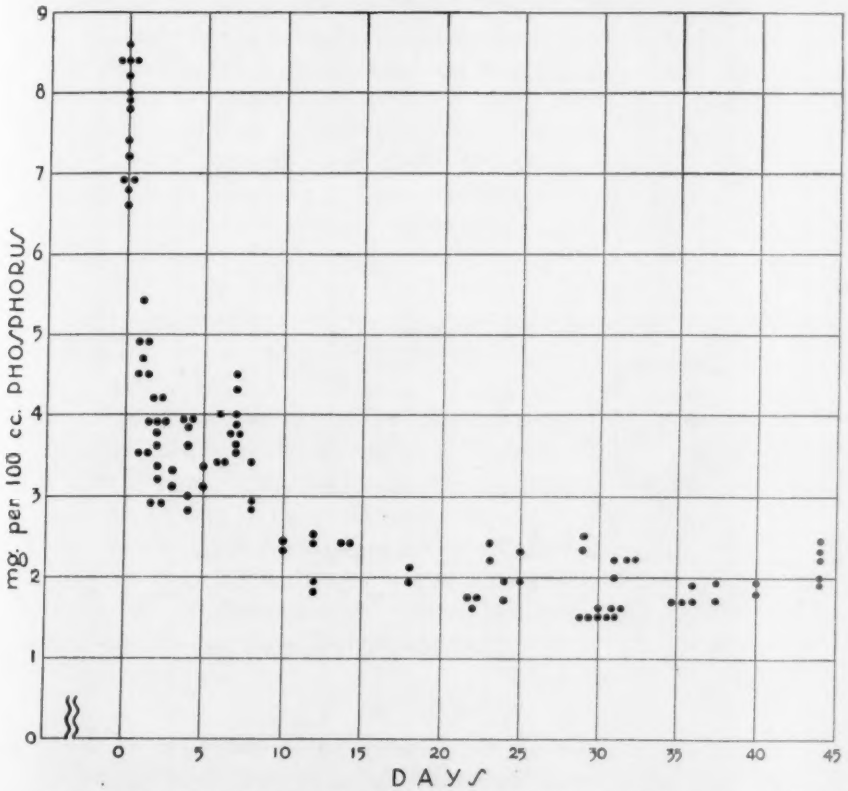

Chart 3.—Representation of the decrease of inorganic phosphorus in rats after they had received a rickets-producing diet.

D, the phosphorus was not reduced below 4 mg. in animals on the rickets-producing diet. This fact is especially noteworthy in view of the rapid effect of this diet on the phosphorus values for normal rats (fig. 3).

Thus, after the administration of a single large dose of viosterol to rachitic rats, there is for the first ten days a slow and steady increase of the phosphorus in the blood, which parallels the degree of healing in the bones. This result is similar to that obtained when repeated small doses were given over a long period of time.

Development of Hypophosphatemia in Rats on a Rickets-Producing Diet.—The method of determining inorganic phosphorus in small amounts of plasma has made it possible to follow the development of the hypophosphatemia in rats fed a rickets-producing diet. Rats which were 3 weeks old were put on a normal standard diet after weaning until their weight was 50 Gm. At this stage the inorganic phosphorus values were about 7.6 mg. Then the rats were put on a rickets-producing diet (Steenbock and Black), and samples of blood were taken on following

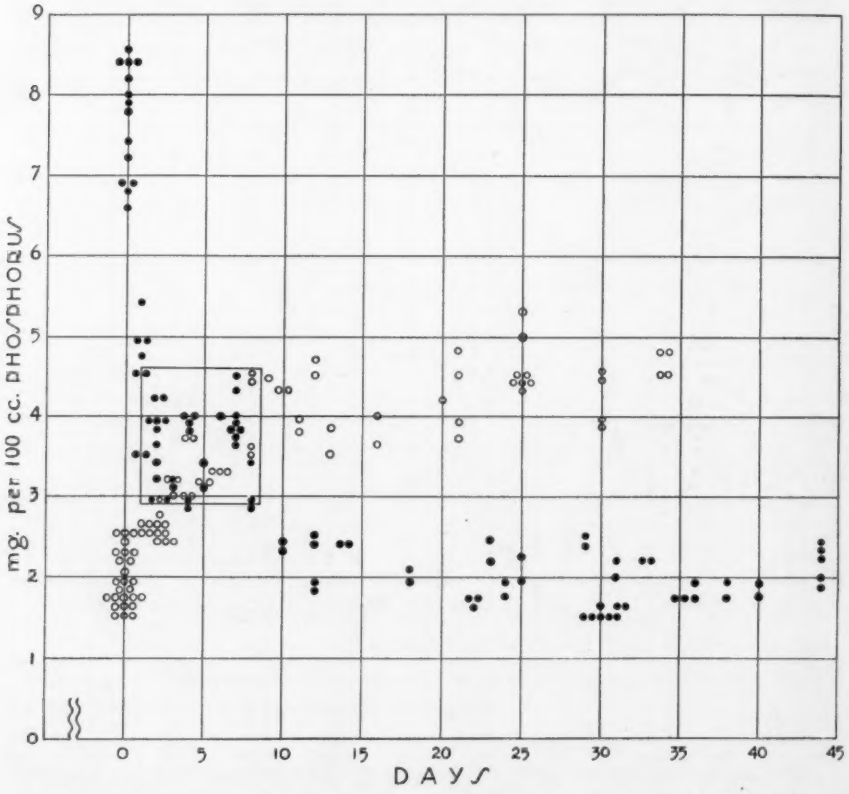

Chart 4.—Composite of the data shown in chart 2 (rings) and chart 3 (dots), showing the common area of phosphorus values in healing and developing rickets, respectively.

days. As a rule, a rat was bled only once or twice. The values found on the respective days after the changes to the rickets-producing diet are compiled in chart 3.

The first marked drop in the phosphorus values could be noted as early as from twenty-four to forty-eight hours after the change in diet, the values averaging about 4.5 mg. Then there was a slow decrease until the twelfth day, when the values usual for rachitic rats were reached.

There was no further change after this time. Even after five weeks the values were about 2 mg.

COMMENT

Experiments were begun in the hope of discovering whether the lack of relationship between the clinical status and the course of rickets and the inorganic blood phosphorus could be explained by a temporary increase of the vitamin D stores, which in turn causes a temporary increase of the phosphorus insufficient to cure the rickets.

My experiments have shown, however, that a single administration of a large dose of viosterol does not bring the inorganic blood phosphorus back to normal if the animals are kept under the original rickets-producing conditions. After ten days, when complete healing of the lesions of the bones is shown by roentgen examination, the inorganic phosphorus has increased to from only 50 to 60 per cent of the normal value for phosphorus in rats. This value, approximately 4 mg., then remains unchanged for weeks, in spite of the continued rickets-producing diet.

This is in contrast to the results, presented in chart 3, of experiments in which rats on a rickets-producing diet showed a decrease of phosphorus to about 2 mg. In chart 4 the data of charts 2 and 3 are combined, and the square indicates an area in which the same phosphorus values are found in both developing and healing rickets. This indicates the lack of significance of a single determination of phosphorus in such a dynamic process as the development or healing of rickets. Since this is true of rats that can be kept under standard conditions, how much more is it true of children in whom these conditions vary from day to day? As Hess and Unger [8] pointed out long ago, only a series of determinations can show the trend of the process.

SUMMARY

The lack of relationship between the blood phosphorus and the clinical findings in children in certain cases caused me to make an experimental study of the changes in the blood phosphorus of rats kept under controlled conditions. Administration of a single large dose of viosterol to rats that have been fed a rickets-producing diet until the phosphorus is reduced to about 2 mg. per hundred cubic centimeters causes a slow increase of the inorganic phosphorus of the blood to about 4 mg. The time relationship of the healing process and the increase of the inorganic blood phosphorus is not clear. The most that can be said is that under the given conditions they parallel one another.

The highest level reached, about 4 mg., which is far below the normal value for phosphorus in rats, is maintained without further administra-

tion of vitamin D if the animals continue to receive the rickets-producing diet which is low in phosphorus and high in calcium.

A rickets-producing diet fed to normal young rats causes a marked drop in the inorganic phosphorus within from twenty-four to forty-eight hours.

The absolute values for phosphorus may be the same at certain times in the process of the development or the healing of rickets. A single determination of phosphorus has therefore little significance in the analysis of experiments or in the treatment of clinical rickets.

In order to facilitate estimations in series with small amounts of blood, a method is described which can be performed with 0.05 cc. of serum or plasma. This method is based on the principle of Kuttner's molybdic acid-stannous chloride reaction.

NOTE.—An article by Bodansky [11] has come to my notice since the completion of this manuscript. He reported corrections for the Kuttner and Cohen method of phosphorus determination and demonstrated deviations from Beer's law which correspond in principle to the corrections used in this paper.

11. Bodansky, Aaron: Phosphatase Studies, J. Biol. Chem. **99**:197, 1932.

EVALUATION OF THE WHITE BLOOD CELL PICTURE IN AMBULATORY CHILDREN WITH POSITIVE TUBERCULIN REACTIONS

SUPRAVITAL STUDIES

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The criteria for gaging activity of the tuberculous infection in the ambulatory child are difficult to evaluate. The need for an adequate appraisal of the pathologic status of the infection in a child with a positive tuberculin reaction is evident. This is particularly of moment in the child whose complaints are few, and in whom a physical examination reveals little that is abnormal.

Many laboratory procedures have been employed within recent years directed toward the determination of activity of a tuberculous focus by examination of the blood. The most common ones in use at present are the determination of the sedimentation rate of the erythrocytes, the Schilling count and the ratio of monocytes to lymphocytes. The first two indicate the changes produced by an infectious process, regardless of etiology. The last, while not entirely specific, is identified more closely than the others with the pathologic changes that take place in the tuberculous focus.

In this paper, further studies are presented of the peripheral blood of the ambulatory child. This phase was touched on briefly in a previous communication.[1] Serial examinations of the blood of a larger number of patients, studied in some instances over several years, are analyzed. A résumé of the more recent contributions bearing on the cellular reactions in tuberculosis is included, in the light of which the results obtained have been evaluated. The object was to detect any relationship that may exist between changes in the peripheral blood picture and the minor degrees of activity following in the course of latent tuberculous infection. For this correlation, it was necessary to weigh the results of physical examination, complaints of the child, the source of infection, the period of exposure, the roentgenogram and the tuberculin reaction. A few published observations have indicated that significant changes occur in the blood following the administration of tuberculin. Consid-

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1. Smith, Carl H.: The Leukocytic Reaction in Tuberculosis of Infancy and Childhood, Am. J. M. Sc. **182**:221 (Aug.) 1931.

eration is also given in this paper to the cellular status of the blood before and after the tuberculin reaction. In this study, as in the preceding one, the supravital technic was employed, and attention was directed not alone to the fluctuations of the monocytes and lymphocytes but to the complete leukocytic response. The monocyte bears emphasis, however, because it is the forerunner of the epithelioid cell which constitutes the morphologic unit of the tubercle.

LITERATURE

Sabin and her co-workers,[2] in 1925, showed that in the rabbit the tubercle bacillus grew and developed within the monocyte of the connective tissues and blood. The epithelioid cell and the Langhans giant cell of tuberculosis were traced as derivatives of the monocytes. Spread of a tuberculous lesion within the tissues was manifested in the blood by a rise in the number of monocytes. Resistance of the animal and healing of the focus, however, were associated with a lymphocytic increase. The ratio of the percentage of monocytes to that of lymphocytes (M/L index), as determined by examination of the peripheral blood, served as an expression of the stage of extension or regression of the tuberculous areas within the tissues.

The results of these studies quickly found their confirmation in their application to cases of tuberculosis among children and adults.[3] That all types of leukocytes enter into the tuberculous reaction was shown by Medlar[4] for adults and by Smith[1] for infants and children. The greater number of investigators, however, have concerned themselves primarily with the leukocytic response in forms of tuberculosis in which the activity was clinically unquestioned. A few studies of the cellular reaction of the blood in latent tuberculosis of childhood have appeared.

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2. Cunningham, R. S.; Sabin, F. R.; Sugiyama, S., and Kindwall, J. A.: Rôle of the Monocyte in Tuberculosis, Bull. Johns Hopkins Hosp. **37**:231 (Oct.) 1925.

3. (*a*) Rogers, P. M.: A Study of the Blood Monocytes in Children with Tuberculosis, New England J. Med. **198**:740, 1928. (*b*) Blackfan, K. D., and Diamond, L. K.: The Monocyte in Active Tuberculosis, Am. J. Dis. Child. **37**: 233 (Feb.) 1929. (*c*) Cunningham, R. S., and Tompkins, E. H.: The White Blood Cells in Human Tuberculosis, Am. Rev. Tuberc. **17**:204 (March) 1928. (*d*) Finner, L. L.: The Clinical Value of the Monocyte Count in Pulmonary Tuberculosis, ibid. **21**:764 (June) 1930. (*e*) Morriss, W. H., and Tan, S. H.: The Differential Leukocyte Count in Pulmonary Tuberculosis, ibid. **16**:729 (Dec.) 1927. (*f*) Flinn, J. W., and Flinn, R. S.: The Leukocytic Picture of the Blood as an Aid in the Prognosis and Treatment of Pulmonary Tuberculosis, ibid. **20**:347, 1929. (*g*) Flinn, J. W.; Flinn, R. S., and Flinn, Z. M.: The Correlation of Blood Counts in 150 Clinical Cases of Tuberculosis, and Underlying Pathologic Changes as Shown by Serial X-Ray Films, ibid. **27**:488 (May) 1933.

4. Medlar, E. M.: An Evaluation of the Leukocytic Reaction in the Blood as Found in Cases of Tuberculosis, Am. Rev. Tuberc. **20**:312 (Sept.) 1929.

Friedman, Dameshek and Hawes [5] pointed out the agreement between the hematologic and clinical findings in the child whose latent focus is situated in the bronchial lymph nodes. They suggested that the changes in the monocyte-lymphocyte ratio following the subcutaneous injection of 0.01 mg. of old tuberculin indicated possible reactivation of a focus of tuberculosis. Hamil,[6] however, found that the tuberculin reaction in cases with involvement of the bone and hilar glands elicited no definite leukocytic changes. Reilly [7] studied the monocytes and lymphocytes of the peripheral blood in thirty-two girls with tuberculosis of the hilar nodes, whose ages ranged from 6 months to 14 years. The results of a six month period of observation showed that clinical activity was associated with a monocytic increase and a lymphocytic decrease, and that with inactivity the reverse cytologic relationship was even more evident. Neither of these investigations, however, included studies of the complete cellular reaction.

The view of Sabin that a symbiotic relationship exists between the tubercle bacillus and the monocyte has been challenged by a number of observers. Gottlieb [8] noted the degeneration of human bacilli in the monocytes. While the studies of Lurie [9] pointed to the destruction of the organisms as a function of the epithelioid cell, their multiplication in an organ is associated with a simultaneous proliferation of monocytes. Long [10] attempted to reconcile these conflicting views by pointing out that the water, oxygen and glycerol content and reaction of the tissues of the host are determining factors in the survival of the tubercle bacilli within the mononuclear cell. Under favorable environmental conditions the monocyte permits survival and multiplication of the bacillus within its confines. Adverse physicochemical states existing in epithelioid cells, however, may be intensified by a hypersensitive state and act to inhibit the growth of the organism within them. These intracellular changes, he indicated, are intimately bound up with varying degrees of immunity.

5. Friedman, E.; Dameshek, W., and Hawes, J. B., 2d: The Examination of the Blood as an Aid in the Diagnosis of Hilum Lymph-Node Tuberculosis, Am. Rev. Tuberc. **25**:24 (Jan.) 1932.

6. Hamil, B. M.: Tuberculosis in Infants and Children: White Blood Cell Counts; Evaluation of the Monocyte-Lymphocyte Ratio by the Supravital Staining Method, Am. J. Dis. Child. **41**:1023 (May) 1931.

7. Reilly, W. A.: The Behavior of the Monocytes in Tuberculosis in Children, Am. Rev. Tuberc. **25**:178 (Feb.) 1932.

8. Gottlieb, R.: The Monocytic Reaction in Tuberculosis, Am. Rev. Tuberc. **25**:172 (Feb.) 1932.

9. Lurie, M. B.: The Correlation Between the Histologic Changes and the Fate of Living Tubercle Bacilli in the Organs of Tuberculous Rabbits, J. Exper. Med. **55**:31 (Jan.) 1932.

10. Long, E. R.: A Chemical View of the Pathogenesis of Tuberculosis, Am. Rev. Tuberc. **22**:467 (Nov.) 1930.

In the analysis of the factors involved in the peripheral blood changes, recent investigations concerning the biologic responses to each of the chemical components of the tubercle bacillus require consideration. Sabin and her associates [11] found that the lipoid fraction of the organism, in particular the phosphatide, is responsible for the production of tuberculous tissue. When this substance is injected intraperitoneally into rabbits, it is possible to trace the development of typical epithelioid and Langhans giant cells from the young connective tissue cells and monocytes of the omentum. The protein fraction, however, is responsible for the fever observed and also acts as a stimulant for the formation of plasma cells. The polysaccharides are chemotactic and toxic to the neutrophilic leukocytes. These investigators regard the epithelioid cell of tuberculosis as the specific reaction toward the tuberculophosphatide, especially when derived from the human strain of the organism. This cell assumes its characteristic cytologic appearance by a process of intracellular dispersion of the lipoid phagocytosed by the monocyte.

Medlar [4] regards the blood picture in tuberculosis as indicative of a cellular response to damaged tissue, rather than a specific reaction to the organism itself. The polymorphonuclear neutrophil in this process is associated with the phase of abscess formation. He does not believe that increased numbers of this cell in the circulating blood are due to mixed infection. In studies involving latent tuberculosis of childhood, it is difficult to conceive that transitory increases in the polymorphonuclear neutrophil are ordinarily related to formation of abscesses. The definite position of the eosinophilic leukocyte is still undetermined. The presence of eosinophils in the blood picture in nontuberculous conditions is usually considered of favorable prognostic significance. Grass and Simmert [12] observed that in tuberculosis of childhood the height of pulmonary infiltration coincides with the most pronounced eosinophilia, and that with regression of the process these cells decrease in number. Their conclusion that this cell bears a relationship to the phenomenon of allergy, or sensitization in tuberculosis, is borne out by many observations.

METHOD

The details of the supravital technic as well as of the description of leukocytes by this method have been clearly outlined by Sabin [13] and Cunningham and Tompkins.[14] The advantage derived from the study of the living cell is greater accuracy

11. Sabin, F. R.: Cellular Reactions to Fractions Isolated from Tubercle Bacilli, Physiol. Rev. **12**:141 (April) 1932.

12. Grass, H., and Simmert, H. V.: Die Rolle der Eosinophilie im tuberkulösen Geschehen, Klin. Wchnschr. **10**:1457 (Aug. 1) 1931.

13. Sabin, F. R.: Studies of the Living Human Blood Cells, Bull. Johns Hopkins Hosp. **34**:277, 1923.

14. Cunningham, R. S., and Tompkins, E. H.: The Supravital Staining of Normal Human Blood Cells, Folia haemat. **42**:257 (Nov.) 1930.

of the count,[15] which is due, in part, to a finer differentiation of cytologic characteristics. The monocyte and its derivatives, which are of primary importance in blood counts of tuberculous patients, are more readily distinguished by the supravital method.

The limitations of this technic, enumerated by Hall,[16] are offset by the fundamental advantages of examining fresh blood when it is subjected to a minimum of trauma. His criticism that the effects of cellular metabolism may alter the specific distinguishing features of the monocyte merits consideration. Adventitious factors, such as the age of the preparation, elevation of temperature and concentration of the stains, as well as the intrinsic physiologic changes in the cell unrelated to tuberculosis, may affect the size and pattern of the neutral red bodies that constitute the characteristic rosette. With these precautions in mind, "stimulated" or "modified" monocytes, resulting presumably from the growth of the tubercle bacillus, are less frequently encountered in peripheral blood. The extreme rarity with which epithelioid cells appear in the blood stream of the tuberculous child, as compared with the blood of the rabbit, may be accounted for by the smaller dosage of infecting organisms in the former. Cunningham[17] also suggested that the loss of motility of the epithelioid cell tends to fix it in the area of proliferation within the tissues, while monocytes enter the blood stream more readily because of their location on the periphery of the tubercles. Clasmatocytes were identified in the examination of the blood even more infrequently. The present tendency is to regard this cell as a physiologic variant of the monocyte.

Briefly, the technic consisted of receiving a small drop of blood on each of two coverslips and allowing them to spread on slides previously coated with nontoxic concentrations of neutral red and vital janus green stains. Specimens of blood obtained during the morning clinic period were examined within two hours under the oil immersion objective in a warm box kept at about 37 C. In the interval, the preparations remained at room temperature. Casey and Rosahn[18] found that the supravital smears were preserved more effectively in the cold, preparatory to examination, than in a hot box. Total leukocyte determinations were carried out at the same time according to the usual procedure.

In each case, the average was recorded of 100 cells counted from each of two coverslips. The importance of counting more than the customary 100 cells cannot be sufficiently emphasized. Barnett[19] recently pointed out the existence of an unavoidable error in the differential count which is based on inherent differences in the cellular content of the small drops of blood removed for examination. While this error can never be entirely eliminated, it can be substantially decreased by counting larger numbers of cells.

In many of the current studies bearing on differential blood counts, each type of leukocyte was recorded only in terms of absolute values. While the importance

15. Smith, Carl H.: Differential White Count in Infancy, Am. J. Dis. Child. **40**:505 (Sept.) 1930.

16. Hall, B. E.: A Critical Review of the Hematologic Literature Dealing with the Results of the Supravital Staining Method, Folia haemat. **43**:206, 1930.

17. Cunningham, R. S.: Jerome Cochran Lecture; Studies on the Pathology of Tuberculosis and Syphilis, J. M. A. Alabama **1**:8 (July) 1931.

18. Casey, A. E., and Rosahn, P. D.: Delayed Differential Counting of the White Blood Cells by a Modified Supravital Technique, Proc. Soc. Exper. Biol. & Med. **28**:658, 1931.

19. Barnett, C. W.: The Unavoidable Error in the Differential Count of the Leukocytes of the Blood, J. Clin. Investigation **12**:77 (Jan.) 1933.

of this added information is fully realized, differential percentages maintain their advantages in being less cumbersome and more readily comprehensible in terms of old established data. It is evident also that with a marked leukocytosis a small percentage of monocytes may be represented by such an increase in absolute numbers as to give a misleading impression of activity. In the present study, both values are included in the tables. The monocyte-lymphocyte ratio was obtained by dividing the percentage or total number of monocytes by the corresponding value of lymphocytes.[3c]

A study which involves quantitative changes in the individual white cells and fluctuations in the monocyte-lymphocyte ratio necessitates a consideration of normal values. In normal infants and children, lymphocytes, for instance, decrease sharply with increasing age, whereas monocytes are reduced to a much less degree. As yet, figures for the various types of white blood cells examined by the supravital technic are limited. From the normal values of monocytes and lymphocytes as stated by Blackfan and Diamond,[3b] and from those of all cells as stated by Smith [1] and Benjamin and Ward,[20] two groups were formed. One included the period from infancy up to 4 years of age; the other extended from 4 to 13 years. Separation of the two groups was made at this age level because values for the respective cellular types show a more pronounced shift at this point, particularly as they apply to the lymphocyte. Again, the infection runs a more acute course in the younger group, while calcification is a more prominent feature in the older child.

The difficulties in judging deviations from the normal are obvious because of the wide range in the number of cells that occur in the peripheral blood of the healthy child. For practical purposes, a modification of the plan suggested by Medlar [4] was followed. Since an increase in neutrophilic leukocytes and monocytes and a decrease in lymphocytes are associated with activity, normal maximum values were established in each age group for the first two types of cells, and a normal minimum value for the last (tables 1 and 2). The basophil was omitted from consideration because it cannot as yet be assigned to any phase in the pathologic process. The eosinophilic leukocyte seems to play a significant part in allergic manifestations of the disease, and its increase in the blood can often be ascribed to this factor. Since the blood in acute cases of tuberculosis in children usually shows complete absence of this cell, a minimum value was set for the eosinophil in considering activity. It is at once apparent that the dividing line between normal and abnormal is arbitrary, but it serves as a practical basis for comparative studies.

RESULTS

The results presented in this paper are based on a study of twenty-three children with the childhood type of tuberculosis, whose ages ranged from 11 months to 13 years. The study was conducted in the outpatient departments of the New York Nursery and Child's Hospital and the New York Hospital during the years from 1929 to 1933, and the cases were followed through a period ranging from one week to two years and ten months. Seventeen of the children were observed for three months and more. For comparative purposes, twenty-one fatal

20. Benjamin, B., and Ward, S. M.: Leukocytic Response to Measles, Am. J. Dis. Child. **44**:921 (Nov.) 1932.

TABLE 1.—*White Blood Cell Counts of Children Ranging in Age from 11 Months to 4 Years*

Types	Total White Cell Count	Polymorphonuclears		Eosinophils		Lymphocytes		Monocytes		Monocytes/ Lymphocyte Ratio	Comment
		Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number		
A. Normal counts: from 11 months to 4 years as a basis for consideration of activity...	**Over 10,000**	**Over 50**	**Over 5,000**	**Under 2.5**	**Under 250**	**Under 32**	**Under 3,200**	**Over 9**	**Over 900**	**Over 0.28**	
B. Ambulatory cases: from 11 months to 4 years; some symptoms and signs											
Extreme.....	4,000-19,500	32-70	1,536-10,720	0-4	0-368	20-59	1,200-5,265	8-27	384-5,265	0.14-1	
Average.....	12,223	55	6,889	0.8	83	29.6	3,402	14.1	1,846	0.48	13 counts in 6 cases
C. Ambulatory cases: from 11 months to 4 years, no signs or symptoms											
Extreme.....	4,500-13,800	25-70	1,675-7,210	0-13	0-1,092	19-63	1,800-6,254	5-19	291-1,794	0.08-0.58	
Average.....	8,711	43	3,747	3.0	276	43.1	3,729	10.2	901	0.24	48 counts in 11 cases
D. Fatal cases: all but three children under 4 years											
Extreme.....	7,280-31,500	49-92	4,950-26,145	0-1	0-900	3-30	365-5,880	3.5-31	406-6,075	0.42-3.66	
Average.....	13,976	73	10,304	0.13	27	12.8	1,732	13.7	1,910	1.1	69 counts in 21 cases; 9 counts in 3 cases (children from 4 to 6 years of age)

TABLE 2.—*White Blood Cell Counts of Children Ranging in Age from 4 to 13 Years*

Types	Total White Cell Count	Polymorphonuclears		Eosinophils		Lymphocytes		Monocytes		Monocytes/ Lymphocyte Ratio	Comment
		Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number		
A. Normal counts: from 4 to 13 years as a basis for consideration of activity.....	Over 8,500	Over 60	Over 5,100	Under 2.5	Under 200	Under 28	Under 2,400	Over 9	Over 750	Over 0.3	
B. Ambulatory cases: from 4 to 13 years, with some signs and symptoms											
Extreme.....	4,900-17,800	47-76	3,102-13,528	0-9	0-1,260	12-42	975-3,850	3-20	441-1,777	0.12-0.95	
Average.....	10,030	62	6,427	3	337	23.8	2,241	10.4	1,021	0.44	15 counts in 7 cases
C. Ambulatory cases: from 4 to 13 years, with no signs or symptoms											
Extreme.....	5,000-15,500	38-76	1,806-9,652	0-23	0-2,162	14-46	1,272-6,200	5-17	336-1,529	0.15-0.71	
Average.....	8,417	54	4,608	4	369	32.0	2,636	9.4	772	0.29	70 counts in 16 cases
D. Ambulatory cases: from 4 to 13 years, showing calcification in roentgenograms and marked reactions to low dilutions of tuberculin											
Extreme.....	4,200-15,500	38-71	1,806-9,174	1-23	52-2,162	17-46	1,666-6,200	5-14	336-1,529	0.15-0.64	
Average.....	8,750	53	4,604	5	504	33.4	2,869	8.5	720	0.25	35 counts in 8 cases

cases of tuberculosis occurring in the younger age group which were studied during the same period were included (table 1).

The absence of pathognomonic signs and symptoms indicative of existing tuberculous infection in childhood renders it difficult to segregate the blood counts of children in whom activity is suspected. Eberson, Delprat and Wolff,[21] in a statistical study of children with positive and negative reactions to tuberculin, observed that none of the usual clinical signs or symptoms had any bearing on diagnosis. Opie and his co-workers [22] demonstrated by roentgenologic examination extensive tuberculous lesions in children without accompanying constitutional reactions or obvious physical signs. The pulmonary infiltrations and calcification of the tracheobronchial nodes noted in the roentgenograms of patients with positive reactions to the Mantoux test are difficult to interpret from the standpoint of activity. Intercurrent nontuberculous infections may not alone evoke suspicions of manifest disease in the patient with a positive reaction, but may produce equivocal roentgenographic changes.

Since the purpose of this study is to present a picture of the peripheral blood in the ambulatory patient with a positive tuberculin reaction, the distribution observed in tables 1 and 2 became necessary. Twenty-four counts not included in these tables were obtained on the day of the positive reaction, and will be considered separately. In both age groups, the counts of the children (tables 1 and 2B) who at the time of examination complained of cough, fatigue, elevation of temperature and sudden unexplained loss of weight, and who on physical examination showed evidences of infection of the upper respiratory tract, the presence of râles or changes in the percussion note, were separated from the larger number (table 1C and D) who had no symptoms. Most of the children of this special group showed a marked reaction after the intracutaneous injection of from 0.01 to 0.2 mg. of tuberculin.

In the younger group (table 1B), the roentgenogram revealed indefinite hilar changes, calcification being uncommon. In one case, however, the reactions of the peripheral blood were surprisingly in accord with the roentgenogram and not with the physical examination. A colored infant of 11 months, brought to the clinic for routine examination, was found to be thriving, and no deviations from the normal were noted physically. With the history, however, that the mother had been recently admitted to a hospital with a diagnosis of tuberculosis, a Mantoux test was applied. Before the injection was made, however, a study of the

21. Eberson, F.; Delprat, J. P., and Wolff, E.: Suspected Juvenile Tuberculosis, Am. J. Dis. Child. **40**:753 (Oct.) 1930.

22. Opie, E. L.; Landis, H. R. M.; McPhedran, F. M., and Hetherington, H. W.: Tuberculosis in Public School Children, Am. Rev. Tuberc. **20**:413 (Oct.) 1929.

blood revealed 24 per cent of monocytes, an absolute count of 3,600 cells and a monocyte-lymphocyte ratio of 0.83. The tuberculin reaction was markedly positive, and the roentgenogram showed evidences of interlobar pleurisy and pulmonary consolidation. The peripheral blood, during one month, showed a moderate leukocytosis, a slight increase of polymorphonuclear neutrophils and an almost complete absence of eosinophils. The monocytes ranged from 11 to 27 per cent, corresponding to absolute values of from 1,331 to 5,265 cells. The lymphocytes were slightly decreased (29 to 32 per cent), and the monocyte-lymphocyte ratios ranged from 0.37 to 1. During this entire period the child appeared well, and when the monocyte-lymphocyte ratio was 1, physical examination gave entirely negative results, and the temperature was only 100.8 F.

Comparison of tables 1 and 2B shows that the more abnormal counts were noted in the younger age groups. This is even more evident from the extreme values than from the average figures. The blood values in the younger children were intermediate between the group without signs or symptoms (table 1C), and the group of fatal cases (table 1D). This observation, although based on a small number of counts, confirms the well known tendency of the primary tuberculous infection to be more severe in early life. Coupled with this is the greater lability of the blood to respond to any type of bacterial infection in infancy and early childhood. In both age groups (tables 1 and 2B), the cellular response comprised an increase in the total white cell count and the number of polymorphonuclear neutrophils and monocytes, a decrease in lymphocytes and an elevated monocyte-lymphocyte ratio. The eosinophils showed a decrease only in the younger group. The entire blood picture constituted, therefore, the reaction of activity. The blood of children with negative reactions to the Mantoux test and severe infections of the upper respiratory tract examined during the period of this study resembled that of the positive group, with the exception of elevated monocyte counts in the latter. In pneumonia, in which the number of monoyctes was found to be increased, the highest values were encountered in children who at the same time had positive tuberculin reactions.

The majority of blood smears comprised those taken on days when the children were entirely well, and when their roentgenograms revealed no marked alterations or evidences of progressive disease. The values (tables 1 and 2C) differed from the normal to such a slight extent that it seemed unnecessary to continue the observations. The relatively normal percentage for each type of cell conformed to the healthy appearance of the child. The reason is quite obvious when one considers that infection had already taken place in each case, and the peripheral blood was being examined to detect the influences of superimposed infection.

Stewart [23] reported from the Lymanhurst School that in an eleven year follow-up of a large group of children who gave positive reactions to the Mantoux test, not a single death could be traced to primary tuberculosis. He pointed out that survival should be expected, with the elimination of reinfection. In the present series of cases, a similar conclusion is justifiable. With the discovery of tuberculous infection in a child by the tuberculin test, investigation for the primary source of contagion was made as a routine. In the majority of cases, elimination of this source had already occurred. With the eventual lack of exposure to open cases, and the added care administered through social service agencies, there was nothing to interfere with recovery from the primary tuberculous infection or to cause its reactivation.

The inability to check completely the exposure to the contact may account for sporadic and unexplained changes in the differential blood count in some instances. In the case of a boy of 3½ years, in which elimination of the open case met with difficulty, the monocytes rose on one occasion to 19 per cent and an absolute value of 1,235 cells, with very slight changes in the rest of the blood picture.

In table 2D are given the blood counts of the older group of children who showed marked reactions to tuberculin in dilutions below 0.02 mg., and whose roentgen examination revealed calcification in the region of the tracheobronchial nodes. This combination required special consideration because, on the one hand, an intense reaction to low concentrations of tuberculin may signify activity, and, on the other, calcification about the hilus is indicative of severe infection. McPhedran [24] observed this lesion most frequently in children who at some time were in close contact with the form of the disease showing positive sputum and who were heavily infected with the organism. It was observed, however, that the blood counts in this group differed little from those in the children without manifest disease. The existence of any degree of residual activity of the infection suggested by the intensity of the tuberculin reaction and by the possible presence of viable tubercle bacilli in the vicinity of the calcifying lesion was not represented by any significant changes in the blood formula. As these blood smears were from children who were in good health and whose welfare was closely supervised, the failure to find any abnormalities was not surprising, particularly since contact with the open case had been broken.

Of interest in this group (table 2D) were two patients whose blood showed an elevation in the number of eosinophils, in one to a maximum

23. Stewart, C. A.: The Evolution of Tuberculosis in the Human Lung, Am J. M. Sc. **185**:346 (March) 1933.

24. McPhedran, F. M.: The Diagnosis and Classification of Pulmonary Tuberculosis in Childhood and Adolescence, Am. Rev. Tuberc. **20**:532 (Oct.) 1929.

value of 10 per cent and in the other to 23 per cent, corresponding to absolute numbers of 1,280 and 2,162, respectively. This increase probably represented an allergic reaction to a factor in the inflammatory process manifested by a few of the children who were rendered hypersensitive by previous infection with the tubercle bacillus. It is still questionable, however, whether the eosinophilia bears a quantitative relationship to the degree of hypersensitiveness, and this, in turn, to resistance. Recently established evidence does not support the view that allergy and immunity in tuberculosis are always coexistent.[25] It can be stated more definitely that a persistent decrease or disappearance of eosinophilic leukocytes from the circulating blood occurs in states of marked activity, and is of unfavorable prognostic import (table 1D).

CHANGES IN THE BLOOD ASSOCIATED WITH THE POSITIVE TUBERCULIN REACTION

The blood smears examined on the day of the positive tuberculin reaction were not included in the foregoing data, and will be considered separately at this point. Recent studies by Bredeck,[26] Friedman, Dameshek and Hawes,[5] and Sullivan and Jones [27] suggested that the blood changes produced by the injection of tuberculin into the susceptible subject may afford a delicate index of the state of focal activity.

From twenty-four blood counts examined on the day of a positive reaction to tuberculin, six of the more striking results are presented in table 3. They represent in more advanced degree the range of variations of the cellular reaction after administration of tuberculin. In a control group of thirteen children with negative reactions to the Mantoux test, whose ages ranged from 1 year to 7 years, the intracutaneous administration of from 0.2 to 2 mg. of tuberculin produced fluctuations in the white cells which differed in no respects from the normal. The case of a 2 year old colored child was omitted from table 3 because a blood count made prior to the Mantoux test was not available for comparison. In this instance, the reaction to 0.2 mg. of tuberculin was markedly positive, with necrosis of the skin. The monocytes comprised 31 per cent of the total number of white blood cells, corresponding to an absolute value of 2,263 cells, half of which were stimulated. During the

25. Rich, A. R.: The Rôle of Allergy in Tuberculosis, Arch. Int. Med. **43**:691 (May) 1929. Friedenwald, J. S.; Rothschild, H., and Bernstein, C.: Allergy and Immunity in Tuberculosis, Proc. Am. Soc. Clin. Investigation, J. Clin. Investigation **12**:969 (Sept.) 1933.

26. Bredeck, J. F.: Tuberculin and the Schilling Blood Differential Count in the Diagnosis and Classification of Tuberculosis, Am. Rev. Tuberc. **27**:377 (April) 1933.

27. Sullivan, M., and Jones, P. H.: Diagnosis of Early Tuberculosis, Am. J. M. Sc. **185**:762 (June) 1933.

TABLE 3.—*Examples of White Blood Cell Counts Associated with the Positive Tuberculin Reaction*

Case	Name	Age	Tuberculin	Date*	Total White Cell Count	Polymorphonuclears		Eosinophils		Lymphocytes		Monocytes		Monocytes/ Lymphocyte Ratio
						Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	
1	T. P.	11 months	0.1	4/ 7/31	12,100	63	7,623	1	121	25	3,025	11	1,331	0.44
				4/ 8/31	11,100	54	5,994	0	0	29	3,219	17	1,887	0.59
				4/11/31	11,100	54	5,994	1	111	29	3,219	16	1,776	0.55
2	D. R.	5 years	0.2	8/25/32	6,600	44	2,904	3	198	40	2,640	13	858	0.33
				8/27/32	7,400	51	3,774	3	222	22.5	1,665	22.5	1,665	1.0
				8/31/32	7,700	53	4,081	4	308	25	1,925	17	1,309	0.68
3	D. S.	7 years	0.2	1/ 3/31	5,300	66	3,498	0.5	26.5	24	1,272	9	477	0.38
				1/ 6/31	5,650	50	2,825	3	169.5	29	1,638.5	17	960.5	0.59
				1/10/31	7,300	69	5,037	0	0	19	1,387	12	876	0.63
4	N. S.	7 years	0.1 mg.	2/14/33	8,400	60	5,040	4	336	28	2,352	8	672	0.29
				2/15/33	9,600	79	7,584	2	192	10	960	9	864	0.9
				2/16/33	6,000	61	3,660	0	0	23	1,380	16	960	0.7
				2/21/33	8,800	51	4,488	2	176	38	3,344	9	792	0.24
5	G. M.	8½ years	0.2 mg.	1/ 4/30	11,000	56	6,160	1	110	36	3,960	7	770	0.19
				1/ 5/30	10,100	78	7,878	1	101	14	1,414	7	707	0.5
				1/ 6/30	10,400	73	7,592	1	104	19	1,976	7	728	0.37
6	T. S.	10 years	0.2 mg.	1/ 3/31	5,500	48	2,640	2	110	35	1,925	15	825	0.43
				1/ 6/31	5,000	35	1,750	1	50	34	1,700	28	1,400	0.82
				1/10/31	5,000	48	2,400	2	100	36	1,800	13	650	0.36

* On the first date in each case the tuberculin was applied. On the following dates the reaction in every instance was markedly positive.

next three months, the monocytes never rose above 10 per cent nor the absolute value above 1,080 cells, and stimulated forms were never again encountered. In this case, as in case 1 in table 3, infection was recent and intensive, and the monocytes rose to the highest levels noted in this series.

With the exception of case 5, table 3, the monocytes were elevated and the monocyte-lymphocyte ratio rose correspondingly. In cases 1 and 3, the increasing ratio was not accompanied by a depression in the number of lymphocytes. Although this cell usually varies in inverse ratio with the monocyte and polymorphonuclear, at times it is independent of either. In case 5, the polymorphonuclear neutrophil was the only cell to show a persistent increase in the course of the tuberculin reaction.

The clinical value of these reactions cannot be appraised with such a small number of cases, except that they exemplify in greater degree the alterations of the blood in the majority of cases. All the children whose blood pictures appear in table 3 were clinically well, but it is noteworthy that in all but case 1 the roentgenogram revealed calcification about the hilus. This lesion, as already mentioned, is indicative of severe infection and may be associated with the presence of living tubercle bacilli. In case 1, that of a child under 1 year of age, pulmonary infiltration and pleuritic involvement were noted in the roentgenogram. The quantity of tuberculin injected, from 0.1 to 0.2 mg., was perhaps higher than was required to elicit a local reaction, but it appears likely that significant cellular responses depend on the use of the increased dosage.

Alterations in the differential count, which depend on a markedly positive tuberculin reaction may throw some light on the reacting capacity of the hypersensitive person. The blood responses obtained after the injection of old tuberculin resembled in large measure those produced by active tuberculous infection. It is conceivable that the cellular reaction produced within the tissues of the hypersensitive child is portrayed in the circulating blood, especially when the local reaction is intense. The peripheral blood, while of no prognostic significance, may still serve as an index to the status of the latent infection, and indirectly as a guide in the clinical management of the patient. Cases which showed an increase in monocytes, such as 1, 2 and 6 (table 3) and the one mentioned as showing 31 per cent of these cells, warrant careful supervision.

The lymphocytes, however, may be moderately elevated in the face of both a rising monocytic count and an increasing monocyte-lymphocyte ratio, as noted in case 3. The lymphocytic variations parallel closely those of the experimental animal, in which this cell appears to be more closely related to resistance, rather than to the peculiar cellular reaction occurring within the tissues. A rise in both monocytes and lymphocytes should be weighed in terms of relative activity and resistance.

A polymorphonuclear increase associated with a lymphocytic decrease, but without any alteration in monocytes, occurs frequently after the administration of tuberculin, although to a lesser degree than that illustrated in case 5. It is usually found in an older child with pronounced local and some constitutional reactions. Doubtless the increase in polymorphonuclear neutrophils would reveal at the same time a shift to the left in the fixed smear. Bredeck [26] utilized this shift, together with the lymphocytic fluctuations, as a basis for classification of activity and healing in adult tuberculosis. This type of cellular response may also be indicative of potential activity, but its final interpretation necessitates more complete studies. It is significant, however, that a polymorphonuclear reaction also is observed in cases of tuberculosis with marked activity (table 1D).

The polymorphonuclear reaction is often probably overlooked because the Mantoux test is usually read within forty-eight hours. Vorwald [28] showed that the initial inflammatory response to the intravenous injection of tubercle bacilli in the rabbit is essentially polymorphonuclear. The site of formation of a tubercle is established by the accumulation of these cells with their ingested organisms. The mononuclear cells subsequently make their appearance, phagocytosing the neutrophilic leukocytes and their bacterial contents, and after eighteen hours dominate the inflammatory reaction. These two phases would probably be observed more frequently if examinations of the blood were carried out at shorter intervals during the course of a tuberculin reaction. These successive responses are illustrated in case 4 (table 3), in which the primary increase of polymorphonuclear neutrophils is succeeded by a rise in monocytes, in both instances associated with a drop in the number of lymphocytes.

COMMENT

The blood picture of the patient with a positive tuberculin reaction is the resultant of the interplay of many basic factors. In many respects, the sequence of events that takes place in the tissues of the tuberculous child finds its parallel in the animal that has been similarly infected. The inflammatory reaction within the tissues following invasion by the tubercle bacillus proceeds, as Opie [29] pointed out, in the same order as with a great many other bacteria, namely, a preliminary response of polymorphonuclear leukocytes succeeded by the production of mononuclear

28. Vorwald, A. S.: The Early Cellular Reactions in the Lungs of Rabbits Injected Intravenously with Human Tubercle Bacilli, Am. Rev. Tuberc. **25**:74 (Jan.) 1932.

29. Opie, E. L.: Cellular Reactions of Tuberculosis and Their Relation to Immunity and Sensitization, Arch. Path. **14**:706 (Nov.) 1932.

phagocytes. The effect of reinfection is to expedite these two phases. The nature of the hypersensitiveness induced by the original infection complicates later cellular reactions. It conditions the effect of the subsequent introduction of tubercle bacilli from an exogenous source, and probably modifies the reactions set up by nontuberculous agents, as in respiratory diseases.

It is still doubtful whether the peripheral blood reflects minutely the fluctuating tissue responses in the day to day progress of the tuberculin-positive child. A single observation, in addition, is of limited significance because of the wide variations ordinarily encountered in the blood counts of normal children. Serial blood counts, however, by establishing a trend for the individual ambulatory patient, often constitute the only means by which stages in the pathologic process may be detected before they become sufficiently pronounced to be recorded in the roentgenogram.

In the inflammatory reaction, the monocyte received particular attention because of its transformation into epithelioid cell and tubercle. Conflicting views have arisen as to the rôle of the monocyte in tuberculosis. Whether the tubercle bacillus grows and multiplies within this cell or is destroyed there, believers in both conceptions agree that during the period of multiplication of the tubercle bacillus a monocytic overgrowth occurs. With the mitosis of monocytes within the tissues, these cells overflow into a general circulation. This was observed in the experimental animal, in the group of fatal cases reported (table 1D) and in the blood of certain ambulatory children (tables 1B and 2B).

Elevations in the number of monocytes and the monocyte-lymphocyte index were more pronounced in the younger than in the older child, and were integrated more closely with the clinical manifestations of activity and the findings in the roentgenogram. The explanation for this difference lies probably in the greater cellular lability earlier in life and the increased tendency for tuberculosis to run a more acute course during this period. It is during the first year of life that the monocytic changes and the monocyte-lymphocyte index of the peripheral blood can be applied to greatest advantage as a guide to the status of the tissue lesion. A persistent elevation in monocytes above the levels indicated in table 2A in the older age group takes on added significance and requires careful inquiry into the causative factors.

The nontuberculous conditions in which the monocytes are increased should be kept in mind in the differential diagnosis. These cells have been noted in increasing numbers in thyrotoxicosis,[80] measles [20] and pneu-

30. Hertz, S., and Lerman, J.: The Blood Picture in Exophthalmic Goitre and Its Changes Resulting from Iodine and Operation: A Study by Means of the Supravital Technique, J. Clin. Investigation **11**:1179 (Nov.) 1932.

monia,[31] at times in rheumatic fever and in von Jaksch's or Cooley's anemia. In the large majority of ambulatory children with tuberculous infection, however, especially in the older group, the monocyte falls within normal range. This may be due to the fact that the lesion is quiescent, or that this cell does not appear in the peripheral blood in increased numbers unless marked overproduction occurs within the tissues.

A lymphocytic increase noted consistently in the blood smear serves as a reliable expression of healing and resistance. In the present study, a high percentage and absolute value of lymphocytes constituted the most common feature of the examination of the blood, and is probably indicative of the tendency toward healing in the childhood type of tuberculosis. Pronounced rises in polymorphonuclear neutrophils and monocytes were usually accompanied by a lymphocytic decrease. This reciprocal relationship is often delayed by the tendency of the lymphocytes to remain elevated until the rise in one of the other cells becomes excessive. So pronounced is the tendency of the lymphocyte to remain at a normal level that a persistent decrease below the limits designated in tables 1 and 2A is indicative of an impairment of resistance, regardless of fluctuations in other types of cells. When this drop is coupled with a marked monocytic rise and consequent upward shift of the monocyte-lymphocyte ratio, a search for causative factors is necessary.

The next stage of added activity includes an increase in polymorphonuclear neutrophils. An elevation of polymorphonuclear neutrophils and a decrease in lymphocytes were observed in the fatal cases noted in table 1D. A similar picture was at times encountered in the peripheral blood at the height of a local tuberculin reaction (case 5, table 3). It is also an essential part of the blood picture of acute nontuberculous disease in children, regardless of sensitiveness to tuberculin. Medlar [4] regarded the polymorphonuclear neutrophil as the cell responsible for formation of abscesses in tuberculosis. This phenomenon, however, is of infrequent occurrence in the childhood type of tuberculosis. An increase in the polymorphonuclear-lymphocytic ratio occurs with febrile manifestations and is the characteristic blood picture of a toxic reaction. In other words, the polymorphonuclear-lymphocytic ratio is significant of a nonspecific inflammatory reaction, as distinguished from the monocyte-lymphocyte ratio, which is the specific reaction for tuberculous disease.

Plasma cells, which Miller [32] found were stimulated by an injection of tuberculoprotein into the rabbit, were not observed in the peripheral

31. Hickling, R. A.: The Monocytes in Pneumonia, Arch. Int. Med. **40**:594 (Nov.) 1927.

32. Miller, F. R.: The Induced Development and Histogenesis of Plasma Cells, J. Exper. Med. **54**:333 (Sept.) 1931.

blood in any of the cases studied. It is as yet difficult to interpret the blood picture of tuberculosis in man consistently in terms of reaction to isolated fractions of the tubercle bacillus.

An exact designation of monocyte and lymphocyte values, and a range of monocyte-lymphocyte ratios that could be utilized as a clinical guide in the supervision of the ambulatory child with a positive tuberculin reaction would serve a practical purpose. The limitations set by a lack of definite clinical standards of activity in the ambulatory child interfere with an accurate derivation of these numerical values, except in acute cases in which activity cannot be questioned. Although the number of observations reported in the present study is small, certain inferences can be made. Sabin [33] stated:

> In a limited clinical experience, we have found that a persistent monocyte-lymphocyte index around one, in which both lymphocytes and monocytes are maintained from 10 to 12 per cent without leukocytosis may well be heeded by the physician, even in the absence of other marked physical signs.

It is interesting to compare these figures with those for the acute cases in table 1D, in which the average percentage of monocytes was 13.7 and of lymphocytes 12.8, producing a monocyte-lymphocyte ratio of 1.1 When this observation is taken in conjunction with the complete data obtained from cases suggestive of activity, search for other evidences of manifest disease is justified when repeated examinations of the blood show 14 per cent or more of monocytes and a percentage of lymphocytes to yield a monocyte-lymphocyte ratio of 0.5 and more (tables 1 and 2 B). These values are, however, subject to modification by larger series of observations. When the blood smear in addition reveals a slight leukocytosis and a rise of polymorphonuclear neutrophils, together with a decrease in eosinophils, the blood picture of activity is strengthened. These cellular percentages, it must be emphasized, are only suggestive, and they must be evaluated in relation to age, and only as a part of the entire clinical picture of the patient.

The individual blood pictures associated with a pronounced local reaction following the intradermal injection of tuberculin appeared to be related to the individual state of reactivity of the infected child. With more extensive data, a classification of the degrees of activity of the latent focus might be attempted, as has been accomplished for adult tuberculosis.[26] Since the development of the adult form of the disease is largely dependent on the peculiar immunologic state induced by the primary infection, the cellular responses after administration of tuberculin may perhaps be of prognostic significance, especially in the older child.

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33. Sabin, F. R.: Cellular Studies in Tuberculosis, Am. Rev. Tuberc. **25**:153 (Feb.) 1932.

The monocytic response after tuberculin may find its explanation in the recent studies of Geiger.[34] It has generally been assumed that there is no natural storehouse for monocytes comparable to that of either polymorphonuclear cells or lymphocytes. Accordingly, increases in monocytes in the peripheral blood have been regarded as resulting from the specific stimulation of reticular cells within the connective tissues. The experiments of Geiger, however, indicate that a reservoir for monocytes exists in tuberculous animals. The injection of colon bacilli into normal guinea-pigs resulted in slight changes in the number of monocytes, whereas a marked increase of these cells occurred after similar inoculation of previously infected animals showing signs of tuberculosis.

It is possible that these observations afford a basis for the unusually high monocyte count noted in the blood of some children with nonspecific infections, such as pneumonia, who give a positive tuberculin reaction. More complete studies are necessary, however, to determine whether this storehouse for monocytes cannot also be established by previous infection with nontuberculous antigens.

A study of the nuclear configuration of the neutrophilic leukocytes serves to complete the peripheral blood picture. While the supravital smear does not lend itself readily to the performance of the Schilling count, the nuclear pattern can be outlined as the cells become less motile. A shift to the left, extending to late myelocyte and metamyelocyte stages, was noted in acute infections during states of activity, and in some children at the time of a marked local tuberculous reaction. This information is fragmentary, however, as comparison with the fixed smear, which is essential, was not carried out in each case.

In the present study, a characteristic cloudy appearance of the supravital blood film, together with the occurrence of degenerating and nonmotile neutrophilic leukocytes, mentioned in another communication,[1] was noted repeatedly in states of varied activity. It was observed at times in the blood of ambulatory children with suggestive activity whose temperature was only slightly elevated. This phenomenon probably bears a relationship to the toxic granulation of the neutrophilic leukocytes noted in pathologic conditions, as well as to an increased sedimentation time. The evidence for the latter rests on the observation of an early deposition of strands of fibrin in the blood smear, and confirms the correlation that is known to exist between increased content of fibrinogen in the plasma and the reduction in the sedimentation time of the red cells.

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34. Geiger, J. T.: A Demonstration that the Reserve Supply of Monocytes Is Increased in Tuberculous Animals, Am. Rev. Tuberc. **23**:76 (Jan.) 1931.

SUMMARY

In a group of twenty-three ambulatory patients with the childhood type of tuberculosis, the white blood cell count was examined periodically with the supravital technic in an endeavor to discover any significant alterations produced by manifest disease.

Since differential percentages vary with age, the results were separated into two groups and compared with similar blood counts of normal children. The age periods extended from infancy to 4 years and from 4 to 13 years.

The peripheral blood of the ambulatory child who was already infected but whose contact with the source of exposure had been broken differed, except for minor alterations, in no wise from the normal. In general, a lymphocytic increase, indicative of resistance, constituted the prominent feature.

The blood count does not perform the function of a diagnostic test in tuberculosis. In periods of suspected clinical activity, however, it at times supplies information of a more precise nature as to the status of the pathologic process than can be obtained from the complaints of the patient, the physical examination or the roentgenogram.

While the cellular changes apply to all age groups, they were most pronounced during activity in the younger child. In the few observations made in this study, the alterations noted in the blood smear differed in degree only from a group of fatal cases of tuberculosis in young children that were studied concurrently.

A tentative monocytic percentage and monocyte-lymphocyte ratio have been suggested to serve as a guide to early manifestations of activity.

Modifications in the white cell picture of the peripheral blood induced by a positive tuberculin reaction require more extended study. It is still problematic whether a comparison of the changes in the blood before and after administration of tuberculin can be utilized to represent the state of focal activity. These changes, however, may possibly serve as an indication of the immunologic status established by the primary infection, and to portray the character of the cellular response in the event of later reinfection.

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DILUTE SNAKE VENOM FOR THE CONTROL OF BLEEDING IN THROMBOCYTOPENIC PURPURA

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In 1916 Kaznelson [1] recommended splenectomy for the cure of essential thrombocytopenic purpura; since then many reports have appeared substantiating the excellent results obtained by him. In the last few years, however, cases in which bleeding continued after splenectomy have been reported by various observers, for example, McLean and his associates,[2] Kasdoba,[3] Lautier, Oberling and Woringer,[4] Bloomfield,[5] Jones and Tocantins [6] and Greenwald.[7] In addition, Whipple [8] reported a series of cases in which a high rate of mortality (87 per cent) resulted because the spleen was removed during the acute stage of the disease; in his report he strongly advised against splenectomy during the stage of active bleeding. Transfusions, too, while they undoubtedly are life-saving measures in cases in which the bleeding is marked and leads almost to exsanguination, frequently have no effect in preventing subsequent hemorrhages; this was true in one of the three cases reported here. In seven other cases previously observed by me a similar experience was encountered, and consequently transfusion, as a method of treatment to effect a cure, has been abandoned. Thus, while cognizant of the fact that splenectomy performed at the proper time and in the properly selected case is still the best method of treatment to effect a permanent cure, one must admit that one is confronted with the disadvantages that some patients continue to bleed after operative intervention, that splenectomy cannot be resorted to in acute cases without a tremendous risk to the patient, and that the operation is not without danger.

From the Pediatric Service of the Israel Zion Hospital.

1. Kaznelson: Ztschr. f. klin. Med. **87**:133, 1919.

2. McLean, S.; Kreidel, K., and Caffey, J.: Hemorrhagic Thrombocytopenia in Childhood, J. A. M. A. **98**:387 (Jan. 30) 1932.

3. Kasdoba: Arch. f. klin. Chir. **166**:794, 1931.

4. Lautier, H. H.; Oberling, C., and Woringer, P.: Rev. franç. de pédiat. **3**:340, 1927.

5. Bloomfield, A. L.: Internat. Clin. **3**:179 (Sept.) 1931.

6. Jones, H. W., and Toncantins, L.: The Treatment of Purpura Hemorrhagica, J. A. M. A. **100**:83 (Jan. 14) 1933.

7. Greenwald, H. M.: J. Pediat. **3**:117 (July) 1933.

8. Whipple, A. O.: Surg., Gynec. & Obst. **42**:329, 1926.

In a recent paper Peck [9] stated:

Experimentation on rabbits has shown that a small amount of moccasin venom given intradermally produces, after an incubation period, a refractory state to the experimental purpura, known as the Schwartzman phenomenon. In an effort to discover whether snake venom could serve as a non-specific method for raising the resistance of vessels to hemorrhage, an attempt was made to treat diseases such as thrombocytopenic purpura, hemophilia, familial hemorrhagic tendencies, and functional uterine bleeding with this substance.

Peck [10] treated three patients with thrombocytopenic purpura who presented such symptoms as epistaxis and purpura; the three patients were treated for from six to nine months and showed definite clinical improvement with a marked decrease in purpura and epistaxis. In one patient the platelet count rose to 200,000; in the other two it was still below 60,000 at the time the report was made.

EXPERIMENTATION

In view of the good results obtained by Peck, it was decided to employ dilute moccasin snake venom in an attempt to arrest bleeding in three cases of thrombocytopenic purpura which were observed during the month of October 1933 and were followed for from six weeks to five months.

All the cardinal signs of thrombocytopenia were present in the three cases: In one no platelets were found on the first examination; in the second the initial count was 10,000, and in the third the count was 75,000. There were prolonged bleeding time, ranging from twenty to fifty minutes, and a nonretractile clot (the clot did not retract at the end of twenty-four hours in any case). The capillary resistance test was strongly positive.

In the three cases there were numerous petechiae, ecchymotic spots and a tendency to bleed from the mucous surfaces. Two patients had severe nosebleeds, and one patient had marked hematuria which lasted four days. The most severe bleeding occurred in the patient with the highest initial platelet count (75,000). This child had a nasal hemorrhage which persisted for eight hours prior to his admission to the hospital. On admission he appeared to be in a state of shock; his pulse rate was 160, and the hemoglobin content was 30 per cent (Sahli). An immediate transfusion of 400 cc. of whole blood was given intravenously as an emergency measure, and a postnasal pack was inserted to control the bleeding. Punctures of the bone marrow were performed on two patients with the following results: In the patient with 10,000 platelets on the initial count, the bone marrow was hyperplastic and contained very few megakaryocytes; in the one with 75,000 platelets the bone marrow had many large megakaryocytes. The spleen was palpable two fingerbreadths below the costal margin in one patient but could not be palpated in the other two children.

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9. Peck, S. M.: Sensitization and Desensitization in Man with Snake Venom (Ancistrodon Piscivorus), Arch. Dermat. & Syph. **27**:312 (Feb.) 1933.

10. Peck, S. M.: Proc. Soc. Exper. Biol. & Med. **29**:579, 1932.

Method.—The venom used was that of a moccasin snake; the initial dose was 0.1 cc. of a 1:3,000 solution in physiologic solution of sodium chloride administered intradermally; this was increased gradually to 0.4 cc. in two cases and to 0.6 cc. in the third case. The injections were given every other day at first, and later, every third or fourth day; the duration of the treatments varied from four weeks to five months.

Peck [10] expressed the belief that the results achieved by snake venom are due partly to the action of the venom directly on the blood vessels and partly to its effect on the mechanism of coagulation. In substantiation of his views he pointed out that good results were obtained in cases with varied etiologic factors, such as functional uterine bleeding, thrombocytopenic purpura and nasal hemorrhage.

Reactions.—In one patient ecchymotic areas which varied in size from 2 to 3 cm. appeared at the site of the injection. In two patients in whom the injections were given only into the forearms, extensive swelling with redness and heat developed several hours after the injection. The redness was present on only a limited area about the site of the injection, but the swelling involved the entire forearm; however, it never extended beyond the elbow or the wrist joints. The reactions were never very painful and rarely lasted longer than forty-eight hours, and they usually appeared after the fifth or sixth injection, regardless of the dosage. No generalized reaction was observed in any child.

Results.—Active bleeding stopped in the three patients after the third or fourth injection. The third patient, who was admitted to the hospital on Oct. 23, 1933, because of a severe nosebleed, had a second severe nosebleed forty-eight hours after admission and required an additional transfusion of 250 cc. of whole blood. No further bleeding took place until November 9, when a slight oozing was noticed. This was easily controlled by packing the anterior nares. The injections, however, were not given to this patient as regularly as to the other two children; in fact, no injections were given from November 2 to November 15. Snake venom was again administered on Novmeber 15 and was given in doses of from 0.4 to 0.6 cc., every second or fourth day until December 3. This patient was no longer under my personal care after December 3, when the administration of snake venom was discontinued. Slight nasal bleeding, however, occurred from time to time after the injections were discontinued. In the other two patients no additional bleeding has been observed since the treatment was started; in the three patients the petechiae and ecchymotic spots disappeared in from seven to eight days; in two children no new cutaneous hemorrhages have been noted during the entire period of observation; in the third a few purpuric spots on the legs were observed on December 17. In two children the capillary resistance test, which was strongly positive at the first examination, became negative after two months.

The bleeding time was reduced to normal in the three cases; in the first case (chart 1) it was reduced from fifty minutes to three minutes after fifty days of treatment; in the second (chart 2), from twenty minutes to five minutes at the end of twenty-four days; in the third

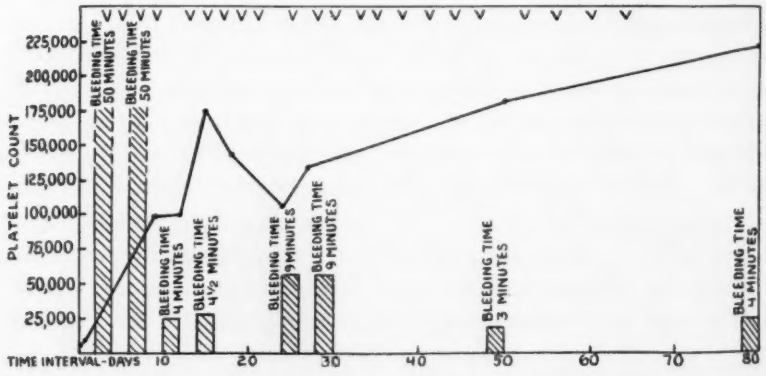

Chart 1.—Reduction in bleeding time and increase in the platelet count over a period of eighty days. *V* represents the intracutaneous injections of snake venom; the solid line shows the number of platelets, and the shaded columns represent the bleeding time.

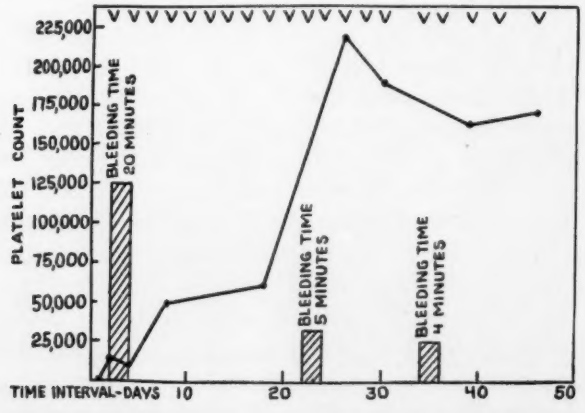

Chart 2.—Reduction in bleeding time and increase in the platelet count over a period of forty-six days. *V* represents the intracutaneous injections of snake venom. The solid line shows the number of platelets, and the shaded columns represent the bleeding time.

(chart 3), from thirty-two minutes to six minutes in ten days and to four and a half minutes in thirty-two days.

In the first case (chart 1) the platelet count rose from 10,000 to 175,000 in fifteen days and reached 220,000 at the end of eighty days; in the second case (chart 2) the count rose from 0 to 220,000 in twenty-

six days but subsequently dropped to 170,000; in the third case (chart 3) the initial count was 75,000 and the value increased to 125,000 at the end of forty-seven days. Two of the patients are ambulant, attend school and follow their usual routine; the third child is still under treatment at the hospital.

COMMENT

The period of observation is too short and the number of cases too small to permit any definite conclusions, particularly in view of the fact that thrombocytopenic purpura is characterized by the occurrence of spontaneous remissions. If, however, snake venom does consistently what it appears to have accomplished in the three cases reported here, it may and should be considered of aid in the treatment of this disease;

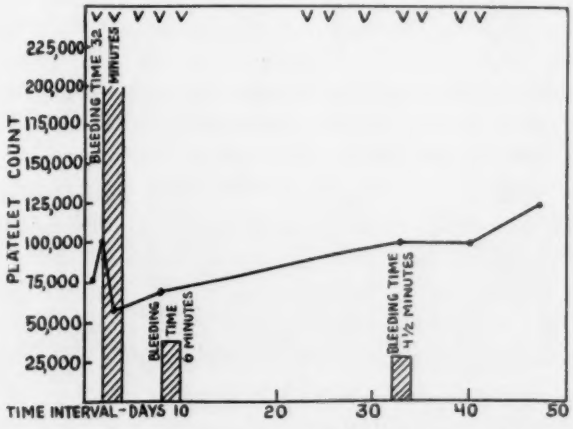

Chart 3.—Reduction in bleeding time and increase in the platelet count over a period of forty-seven days. *V* represents the intracutaneous injections of snake venom; the solid line shows the number of platelets, and the shaded columns represent the bleeding time.

it appears to be of definite value in the control of active bleeding. It is generally believed that a reduction in the number of platelets is not alone responsible for the bleeding and that an increased permeability of the capillary wall is an important additional factor. It is therefore necessary in the treatment of bleeding in thrombocytopenic purpura not only to increase the number of platelets but to decrease the capillary permeability. According to Peck,[10] snake venom achieves the results of acting directly on the blood vessels. The fact that a marked increase in the number of platelets occurred in two of the patients cannot necessarily be attributed to the action of snake venom, since spontaneous increases do occur. An increase in the number of platelets alone is not always followed by a

cessation of bleeding; for example, Brieger [11] observed severe hemorrhages in patients with a relatively high platelet count, and vice versa. When one considers, on the one hand, that, in a small series of eight patients previously treated by various methods before the advent of the use of snake venom, one patient died of a cerebral hemorrhage in the acute stage of the disease after five days of hospitalization, a second bled to death in spite of splenectomy and another died one hour after the spleen had been removed, in spite of four or five transfusions given before operation, and, on the other hand, that injections of snake venom appeared to control active bleeding in the three cases reported here and had no bad after-effects, it appears that the results are sufficiently good to warrant a further trial of this method. It should be emphasized, however, that the use of snake venom is not proposed as a method of cure for thrombocytopenic purpura but rather as a measure to control active bleeding.

SUMMARY

1. Of eight patients treated by splenectomy and repeated transfusions during the years from 1928 to 1932 inclusive, two died of cerebral hemorrhage and one of postoperative shock.

2. Three patients were treated in 1933 with intradermal injections of diluted snake venom; active bleeding was controlled rapidly in every case. No further bleeding occurred in two children; one patient, who was almost exsanguinated on admission to the hospital and who did not receive the injections regularly, manifested oozing from the nasal mucous membranes six weeks after the beginning of the treatment.

3. Snake venom is recommended as a means to control active bleeding in thrombocytopenic purpura.

11. Brieger, quoted by Baar, H., and Stransky, E.: Die klinische Hämatologie des Kindesalters, Vienna, Franz Deuticke, 1928, p. 345.

THE ADOLESCENT HEART

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AND

MAURICE H. ROSENFELD, M.D.

LOS ANGELES

In recent years the study of heart disease has received an enormous impetus, and a keen interest in it has been shown by the laity as well as by the members of the medical profession. Most of the statistics and reports have to do with organic heart disease, and little, if any, attention has been given to the normal adolescent heart. Our interest in the adolescent heart was aroused by our experiences in the center for the diagnosis of heart disease of the Yale Street Clinic. Many times children were referred to us with a diagnosis of heart disease which was based on disturbances in rhythm, murmurs or subjective symptoms. Frequently a single examination was sufficient to differentiate between functional and organic heart disease, but occasionally repeated examinations over a period of years were necessary before a definite conclusion could be reached. It therefore became particularly obvious that the family physician, who sees the child first, should carefully evaluate all his observations before making a positive diagnosis of organic heart disease and, because of this diagnosis, condemning the child to a life of cardiac invalidism.

This study is based on observations on 2,840 children, examined during a period of eight years. Some were examined only once, while others returned to the clinic over a period of from one to four years. The diagnosis of adolescent heart was made in 254 children, or about 9 per cent. There were 92 male and 162 female patients; their ages were between 9 and 16 years. In this climate we are inclined to include in the adolescent period the ages from 11 to 16 years. The division of adolescence into preadolescence, adolescence and postadolescence does not seem to be of importance.

SYMPTOMS

During the adolescent period there is a tremendous change in the function of the endocrine system, a change in the growth and development of the internal organs and an excitation of the sympathetic nervous system. It is due to this rapid physiologic development that many

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functional disturbances are noted, and the great danger arises from misinterpreting certain of these changes as evidence of organic failure. Outstanding as a causative factor in the production of some of the borderline symptoms is the instability of the sympathetic nervous system, many children showing definite sympatheticotonia. It is noteworthy that the number of symptoms is out of all proportion to the physical findings. They are the same as those usually associated with organic heart disease. The various complaints merit a more detailed discussion than a mere mention of their numerical occurrence. They will be taken up in the order of frequency.

TABLE 1.—*Number of Subjects with Adolescent Heart in Each Age Group*

Age, Years	Number of Subjects
9	1
10	14
11	30
12	41
13	45
14	56
15	42
16	25
Total	254

TABLE 2.—*Frequency of Symptoms Chart*

Symptom	Occurrence
Palpitation	123
Fatigue	99
Dyspnea	83
Pain	80
Vertigo	57
Sweating	41
Cyanosis	28
Epistaxis	23
Cough	21

Palpitation.—This occurred in 123 cases. It was evidenced either as a subjective or as an objective finding. Subjectively, the child was conscious of his heart following slight exertion, nervousness, fright or fatigue. Not infrequently the symptom was associated with precordial pain, a feeling of constriction in the chest or shortness of breath. At times it was accompanied by nausea and vomiting. Objectively, there was frequently a heaving precordial impulse, accompanied by a murmur. The type and character of the latter will be considered under a separate heading. The heaving precordial impulse was usually found in children whose physical development was below par. No enlargement was noted in any of the children considered in this adolescent group. The rate was labile and was easily influenced by inspiration, expiration and change of position. In organic heart disease the rate is not so easily influenced by vagus stimulation.

Fatigue.—This sign, which occurred in 99 cases, was expressed as letting down of the general physical stamina of the child and an inability to play as long or as hard as his comrades—or, in the other extreme, as an indifference to play and a preference for quiet. A child in the latter group was frequently irritable, nervous and unreasonable and in some instances demanded considerable attention from his parents. This symptom appears early in the adolescent period.

Dyspnea.—Dyspnea occurred in 83 cases. Shortness of breath varied from simple, frequent sighing to labored respiration on slight exertion. It was never noticed as true cardiac dyspnea with the patient at rest or during the physical examination. It was a complaint, not an actuality. It occurred after an exercise tolerance test and did not last beyond the period in which the heart returned to its normal rate.

Pain.—This was an indefinite symptom which occurred in 80 cases. The pain, as described, was fleeting and was precordial or in either the right or the left side. It was frequently brought about by running or was called "growing pains." Its type and character never resembled the real pain of organic heart disease or angina pectoris. It was never sharp or disabling, and not infrequently a history of such pain was elicited only by interrogation.

Vertigo.—This was mentioned as a symptom 57 times. However, the description of vertigo, or what the patient meant by it, was so indefinite that it cannot be considered as an absolute symptom.

Sweating.—This occurred in 41 cases. It was usual to find sweating in children in whose cases a diagnosis was made of adolescent thyroid disturbance. The observation was noted in 75 children, or in nearly 30 per cent of the total number of children with adolescent heart. The diagnosis of adolescent thyroid disturbance was made on the basis of the presence of an enlarged thyroid gland, palpitation, nervousness, sweating, tremor and, in some instances, blood pressure slightly higher than normal for the child's age. All the children had normal basal metabolic rates. The thyroid disturbance occurred in both sexes, but more frequently in girls than in boys. Thirty per cent is such a high incidence that it merits definite further investigation from the standpoint of the possibility of endemic thyroid activity in this community. This endocrine condition seemed to persist, in many instances, far into the period of development before it gradually subsided. The occurrence of true thyroid disease or hyperthyroidism was infrequent in the total number of children examined. The frequency of active thyroid symptoms and their persistence during the adolescent period is somewhat paradoxical when considered in the light of the low percentage of actual thyroid disease noted in the entire group of children examined. While this is neither the time nor the place to theorize on its etiology, the pos-

sibility that adolescent thyroid activity is a factor in producing many of the so-called cardiac symptoms during the adolescent period should not be underestimated.

Cyanosis and Cough.—Cyanosis occurred in 27 children and cough in 21. They were purely subjective symptoms and were never severe enough objectively to be considered seriously.

Fainting.—This occurred in 21 cases. Some children had typical spells in the clinic during the examination. We concluded that the attack always had a psychic or neurotic basis.

OBSERVATIONS ON THE HEART

In the entire series no child was considered in the group whose heart was proved to be enlarged either on physical or on roentgen examination. It was frequently noted that the overacting heart gave rise to an increased precordial or apical shock which, on palpation, could easily be mistaken for a thrill. In the same type of heart in an undernourished child there was also a visibly exaggerated apical impulse which varied from a local increased thrust in the normal position to a wavy impulse or a heaving of the entire precordium.

Paul White [1] issued this warning with reference to functional murmurs:

> Heart murmurs may be temporary and due to relatively unimportant functional disturbances. It is of great importance to recognize and remember that most systolic murmurs do not indicate the presence of any organic heart disease. Nevertheless, serious diagnoses and bad prognoses have frequently been made, largely on the basis of such murmurs. On the other hand, it should be recognized that even slight systolic murmurs, except in the pulmonic valve area, are not normal; they demand study as to their cause. . . . These facts require the application of study and common sense to the interpretation of murmurs and avoidance of the extreme views, with overemphasis and underemphasis, which have held sway during the swing of the pendulum in the past generation.

During adolescence, a systolic murmur is encountered frequently. We found the symptom in 106 children in our group, or 42 per cent. The types of systolic murmur encountered were: apical, 63 cases; pulmonic, 37, and apical and pulmonic, 6. The apical murmurs were well localized and were not transmitted. We made no effort to give a numerical value to the tone or intensity of the murmurs, as described by Dr. Samuel Levine, as we believe that it is impossible to give a numerical value to a personal equation. The murmurs varied from soft, low-pitched blowing sounds to high-pitched, rough, rasping or musical sounds. They occurred early in systole or in midsystole,

1. White, Paul: Heart Disease, New York, The Macmillan Company, 1931, p. 103.

between the first and the second heart sound, which were always audible and were never replaced by the murmur. It was also noted that in many instances the murmur was influenced in tone, character and intensity during the respiratory cycle by a change of position or by any factor that increased the heart rate.

In many cases the murmur was discovered on the first examination. It varied in tone and in intensity from time to time, and there were intervals during which it was not heard. In some instances the child was followed over a period of years, and it was noted that the murmur disappeared. In others, the murmur persisted without other evidence of cardiac change. For children with a constant systolic murmur, a period of two or three years of observation was required, during which time all evidence of organic heart disease was ruled out by means of physical examination, roentgenograms and electrocardiograms. Only after this check-up were we able, in questionable cases, to decide that the murmur was purely functional.

A pulmonic or basal murmur, systolic in time, occurred in 37, or 14 per cent, of the total number of cases reported. The disturbance was considered as functional only in those cases in which no subjective or objective evidence of congenital heart disease could be found.

Changes in the heart sounds occurring with or without murmur were noted as follows: splitting or reduplication of the first sound, 26 times, and reduplication of the second sound, 25 times. These changes in either the first or the second sound during the period of adolescence are incidental and of no pathologic significance. Furthermore, they were found in children in the early period of adolescence and disappeared as they grew older. Occasionally the reduplications simulated the physiologic third heart sound. In these cases it was necessary to differentiate between the functional element and the presystolic gallop of the first sound found in early mitral stenosis.

Wolferth and Margolies [2] stated:

> The reduplicated second sounds are easily differentiated from proto-diastolic or summation gallop rhythm and physiological third heart sounds by the following characteristics:
>
> (*a*) Reduplication of second sounds may occasionally be well heard at the apex, but its maximum audibility is at the base and rarely as low as the fourth interspace.
>
> (*b*) Second sounds are shorter, sharper, and higher in pitch than gallop sounds.
>
> (*c*) The intervals between the two components of split second sounds are appreciably shorter than those between second sounds and gallop rhythm.

Electrocardiograms were made for 138 of the total group of 254 patients, the standard technic being used. We made no effort to estimate the average rate, as it was noted that in many instances the

2. Wolferth, C. C., and Margolies, A.: Am. Heart J. **8**:459 (April) 1933.

rate in lead I was out of all proportion to the rate in lead III. We feel that owing to the evident excitable state of the child while having an electrocardiogram made, any attempt to estimate an average heart rate for children must be considered as inaccurate.

Evident sinus arrhythmia was found in 54 electrocardiograms, or 25.5 per cent. The degree of sinus arrhythmia varied with the rate and not with the age or sex.

Ventricular premature beats were found in only 1 electrocardiogram. Premature beats were diagnosed clinically in 5 cases. It may be that the increase in rate at the time the tracing was taken prevented its occurrence and registration on the tracing. This small number shows that while extrasystoles are infrequent, they do occur during adolescence, and their presence should not be interpreted as an expression of heart disease.

TABLE 3.—*Incidence of Abnormal Rhythm*

Preponderance						Rhythm				
Right		Left		None		Sinus Arrhythmia		Tachycardia,	Bradycardia,	Premature Beats,
No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	No.	No.
22	16.6	27	19	79	57	54	46	20	1	1

TABLE 4.—*Electrocardiographic Observations*

High QRS Complex		High T Wave		T_3 Inverted		T_3 Flat		High P		Inverted P_3	
No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
64	46	63	45	22	15.8	26	18.8	14	10	6	5

Bradycardia with a rate of 60 occurred only once. A constant rate, above 120 in all three leads, was considered as evidence of tachycardia. It occurred in 20 cases. From this it will be noted that the ratio of the incidence of tachycardia to that of bradycardia in adolescent children is twenty to one. All slow rates should, therefore, be checked by the electrocardiogram to prevent overlooking the presence of various types of heart block or other disturbance in the conducting system.

In estimating the amplitude of the Q R S complex, we adopted 12 mm. as the standard, as recommended by Pardee.[3] R_2 was used, since it gives the highest deflections. In our series, 64 electrocardiograms, or 46 per cent of 138 tracings, showed an R_2 above the average. This was a surprising observation in view of the fact that C. Bruce

3. Pardee, H. E. B.: Clinical Aspects of the Electrocardiogram, ed. 3, New York, Paul B. Hoeber, Inc., 1933, p. 35.

Perry,[4] in his study of a series of electrocardiograms of school children reported comparatively low voltage Q R S complexes. His observations were made on younger children than those included in our group. The increase in amplitude may be explained by the general increase in the normal physiologic processes of the adolescent child, the increase in the nutritional state of the heart muscle and the increase in the physical and mental activity of the child.

Notching and slurring of Q R S III, as noted by Perry, was infrequent in our series.

With the high amplitude of the Q R S complex in the adolescent heart, another outstanding observation was the frequency of the high T wave. If one considers the upper limit of normal as 5 mm., as noted by Pardee and Lewis,[3] in 63 cases, or 45 per cent, the T wave was at or above the upper limit of normal. This unusual percentage of high T waves may be accounted for by the fact that we were dealing with younger persons, while previous observations were based on subjects who had reached maturity. In a general way the number of high T waves paralleled that of the high Q R S complexes, namely 64 instances, of a high Q R S complex and 63 of a high T wave. The inverted T_3 was encountered in 22 cases, or 15.8 per cent. The flat T_3 was encountered in 26, or 18.8 per cent. A review of the P R interval showed no variation from the normal. The short P R interval frequently observed in early childhood was not evident in our group. The P wave was found to be over 3 mm. high in 11 cases. The height of the P wave apparently bears no relationship to the height of the Q R S complex or the T wave.

Axis deviation was determined according to the principles of Carter, Richter and Greene.[5] We found right axis deviation in 22 cases, or 16.6 per cent, left axis deviation in 27, or 19 per cent, and no deviation in 79, or 59 per cent.

COMMENT

It should be stressed that all the symptoms and physical findings observed in the children examined were but functional disturbances occurring during the period of adolescence, and that they were probably produced by the unstable nervous system or by rapid physical development. The findings were most frequently a temporary or a fleeting disturbance, but occasionally they persisted throughout the entire period of adolescence. When the parents and the child were convinced that the symptoms, such as dyspnea, palpitation and precordial pain, were not due to organic heart disease, the child quickly became symptom-free.

4. Perry, C. Bruce: Arch. Dis. Childhood **6**:259 (Oct.) 1931.

5. Carter, E. P.; Richter, C. P., and Greene, C. H.: Bull. Johns Hopkins Hosp. **30**:162 (June) 1919.

When the symptoms had been greatly impressed on the child, it was necessary to increase physical activities slowly and to overcome gradually the fear of the symptoms.

The type and character of the functional systolic murmurs found during adolescence have been described. As the children were reexamined over a period of years, it was noted that usually the murmur disappeared. When the murmur persisted, the child was requested to return for observation for a period of from two to three years. Organic heart disease was ruled out by means of complete physical examination, roentgenograms and electrocardiograms, all of which failed to show evidence of change in the size of the heart, the type of murmur or any other evidence on which the diagnosis of organic heart disease could be based. Because of the lack of definite changes we felt justified in classifying these in the condition known as adolescent heart. Splitting of the first heart sound and reduplication of the second heart sound sooner or later disappeared.

CONCLUSIONS

A statistical and clinical study has been made of 254 children between 9 and 16 years of age.

The subjective symptoms presented were the same as those usually considered as being present in patients with organic heart disease.

The solitary observation of an apical systolic murmur in the adolescent child is not sufficient evidence on which to base the diagnosis of organic heart disease.

The outstanding electrocardiographic findings were the frequency of Q R S complexes and of T wave of high amplitude.

The heart is greatly influenced during the rapid physiologic changes associated with adolescence. Many functional disturbances are noted during this period.

During the adolescent period the diagnosis of early organic heart disease is made too frequently on uncertain data. The differential diagnosis can be made only by the careful evaluation and analysis of all of the data obtained, and in some instances a definite opinion should be given only after several years of careful observation.

CIRCULATION TIME IN NORMAL CHILDREN

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The circulatory system of the normal person provides the body tissues with an adequate supply of oxygenated blood. Under basal conditions the rate at which blood flows to the points of utilization is obviously a determining factor in the adequacy of this supply. It was recognized early that a measurement of the velocity of blood flow would give valuable information as to the efficiency of the circulatory system. The speed of the blood flow is not the same in different parts of the circulatory system because of the differences in gravity and the variations in the size of the capillary bed (there is a marked increase peripheralward). Nevertheless, if the velocity is determined between any two points in the body, this value can be established as a standard. Though not an absolute representation of the rate of blood movement throughout the circulatory system, determinations of the rate between similar points in patients with deranged circulation may be compared with this standard, and valid deductions drawn.

The underlying principle of the many clinical methods which have been suggested to determine the velocity of blood flow between two points is the introduction into the circulatory system at one point of a substance the presence of which can be detected objectively or subjectively at another point in the blood stream. A review of the various methods described until 1931, with a complete discussion of theoretical considerations, appeared in a monograph by Blumgart,[1] who has made many important contributions in this field.

Since the appearance of Blumgart's paper, additional methods, which have the advantage of simplicity and ready application at the bedside, have been published. Winternitz, Deutsch and Bruell [2] introduced the use of sodium dehydrocholate, a bile salt which when administered intravenously produces a bitter taste on the tongue. Fishberg,

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1. Blumgart, H. L.: The Velocity of Blood Flow in Health and Disease, Medicine **10**:1, 1931.

2. Winternitz, M.; Deutsch, J., and Bruell, Z.: Eine klinisch brauchbare Bestimmungsmethode der Blutumlaufzeit mittels Decholininjektion, Med. Klin. **27**:986, 1931; **28**:831, 1932.

Hitzig and King [3] determined the circulatory rate by injecting a solution of soluble saccharin intravenously. The end-point with this drug is a sweet taste on the tongue. With both of these methods the circulation time is measured between the point of injection, an arm vein, and the tongue, where the sensations of bitterness or sweetness are experienced. Neither drug causes unpleasant secondary reactions. Both have fairly distinct end-points. The tests can be repeated after a short interval without loss of accuracy and without danger.

There are no observations on the circulation time in normal children. Congestive heart failure due to rheumatic cardiac disease and congenital abnormalities of the heart are common in children. It seemed important to establish standards in the younger age groups, up to 16 years.

The saccharin method appeared most suited for studies on children because of the nature of the sensation signaling the end-points. Even young children can identify sweetness, and there is the added advantage that the anticipation of this pleasurable sensation does not arouse fears or create apprehensions which may interfere with the accuracy of the responses.

METHOD AND MATERIAL

One gram of chemically pure powdered, soluble saccharin was dissolved by being heated in 1.5 cc. of distilled water. This was most easily accomplished by placing this amount of saccharin in a sterile test tube, adding the distilled water and heating the mixture over an alcohol lamp or a Bunsen burner until the solution was clear. Boiling beyond this point had to be avoided, as evaporation of too much water caused the saccharin to recrystallize. (Such a solution is likely to cause pain or thrombosis when it is injected.) It was poured out of the tube into a sterile medicine glass and drawn up into a 5 cc. syringe after it had cooled to room temperature. The dose of 1 Gm. was employed for children weighing about 100 pounds (45 Kg.) or less. One and one-half grams was used for children weighing over 110 pounds (50 Kg.). The dose for adults was 2.5 Gm. The resulting solution, which amounted to about 2 to 2.5 cc., was injected into an antecubital vein made prominent by a short period of constriction of the arm with a tourniquet. The injection was given through an 18 gage needle with the subject in the recumbent position. The children rested from one-half hour to two hours before the tests.

Invariably, when the child was placed on the examining table preparatory to receiving the injection, tachycardia occurred. To reduce the element of fear, which caused the acceleration of the pulse rate, we allowed the next test subject to view the procedure as it was being done on his colleague. In addition, a pause was taken after the needle was introduced into the vein and before the injection was made. During this period the child was assured that there would be no more pain, and that all that was in store for it was a sensation of sweetness on the tongue "like candy." The child was instructed to cry out "sweet" or "now"

3. Fishberg, A. M.; Hitzig, W. M., and King, F. H.: Measurement of the Circulation Time with Saccharin, Proc. Soc. Exper. Biol. & Med. **30**:651 (Feb.) 1933.

as soon as he experienced the sensation. The injection was made rapidly, and a stop-watch was started when about one half of the solution had been delivered (one-half second). The time at which the child indicated the arrival of the saccharin in the tongue was recorded. The subjects cooperated well and gave prompt answers. That the responses were accurate could be checked in an interesting way, especially with the younger children. Because the sensation of sweetness came as a shock, a grimace would appear on the child's face. Simultaneously he would cry out "sweet."

We can confirm the claim of Fishberg, Hitzig and King that the injection of saccharin as described is not attended by any untoward effects. In no instance were there constitutional sequelae. In two cases not included in this report paravenous infiltrations occurred owing to technical difficulties. In one of the patients an ulceration in the skin and phlebitis resulted.

The children (one hundred in number) were from the Hebrew Orphan Asylum. They ranged in age from 8 to 16, with equal numbers of boys and girls, and were free from cardiac or pulmonary diseases.

RESULTS

The circulatory rate (arm-to-tongue time) in the one hundred normal children from 8 to 16 years of age ranged from 5 seconds to 13.5 seconds. The average was 8.6 seconds. Eighty-three (83 per cent) of the responses occurred after between 6.5 and 10 seconds.

The individual tests giving the age, weight and pulse rate of the subjects are presented in table 1. The results are pictured graphically in the chart and summarized in the table which is set into the chart.

In the few cases in which the test was repeated on the same subject variations in readings usually did not exceed from 1 to 2 seconds. In other instances identical values were obtained. The second test of a repeat is not included in this report.

Because of the comparatively limited number of tests an accurate analysis of the relationship of the age, the pulse rate and the circulation time does not establish a reliable conclusion. From a scrutiny of table 1 it appears that in the younger children, from 8 through 10 years of age, the pulse rate was likely to be accelerated, and, conversely, the circulation time was more often below the average; i. e., the velocity of the blood flow was increased. In the older children, from 14 through 16 years of age, the pulse rates were nearer normal, and the circulation time was more often above the average. We recognize that from the observations in this report such an association is only suggested.

COMMENT

There are no published records of studies of circulation time in normal children. Tarr, Oppenheimer and Sager [4] tested fifteen chil-

4. Tarr, L.; Oppenheimer, B. S., and Sager, R. V.: The Circulation Time in Various Clinical Conditions Determined by the Use of Sodium Dehydrocholate, Am. Heart J. **8**:766, 1932.

dren with cardiac disease ranging from 10 to 14 years of age. In six children with well compensated cardiovalvular disease the average arm-to-tongue time by the sodium dehydrocholate method was thirteen seconds. In the cases of congestive heart failure the values were pro-

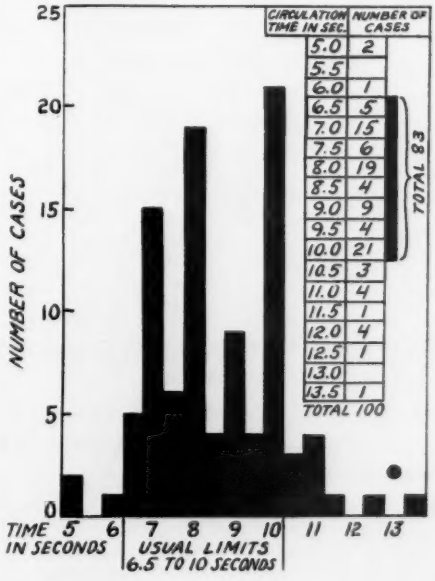
TABLE 1.—*Results of Individual Tests in One Hundred Patients*

Age	Weight, Pounds	Pulse Rate	Saccharin, Gm.	Circulation Time, Seconds	Age	Weight, Pounds	Pulse Rate	Saccharin, Gm.	Circulation Time, Seconds
8	44	108	1	7.5	12	67	120	1	6.5
8	52	120	1	7	12	69	108	1	8
8	55	120	1	7	12	69	108	1	6
8	55	84	1	8.5	12	78	120	1	10
8	55	96	1	10	12	81	84	1	12
8	55	120	1	10	12	82	108	1	7.5
8	56	108	1	7	12	85	108	1	10
8	59	108	1	10	12	85	132	1	9.5
8	62	108	1	7	12	100	96	1	9
9	54	144	1	7	12	119	84	1	12
9	54	90	1	9	12	128	96	1.5	12.5
9	55	96	1	11	13	79	96	1	8
9	59	132	1	10	13	81	96	1	8
9	59	110	1	7	13	84	96	1	10.5
9	60	98	1	8.5	13	87	108	1	7.5
9	62	108	1	10	13	88	120	1	11
9	62	100	1	8	13	89	90	1	8
9	63	120	1	7	13	89	108	1	8
9	65	85	1	6.5	13	90	100	1	10
9	69	120	1	5	13	92	85	1	9
9	77	132	1	5	13	93	108	1	8
9	80	72	1	8	13	94	88	1	11
10	55	80	1	11	13	95	96	1	8
10	56	120	1	6.5	13	99	84	1	10
10	59	110	1	7	14	79	108	1.5	10
10	60	88	1	9.5	14	90	96	1	8
10	60	90	1	7.5	14	93	96	1	7.5
10	64	88	1	9	14	95	108	1	8
10	64	108	1	10	14	97	90	1	7
10	64	72	1	8.5	14	101	96	1.5	10
10	67	96	1	10.5	14	108	86	1	9
10	73	100	1	7	14	114	96	1	9
10	76	100	1	12	14	115	90	1.5	10
11	56	96	1	8	14	118	120	1.5	8
11	65	120	1	7	14	136	84	1.5	12
11	67	96	1	8	15	78	144	1	7.5
11	73	80	1	10	15	90	90	1	9
11	73	80	1	10	15	97	108	1	10
11	75	96	1	7	15	100	72	1	10
11	78	80	1	8	15	102	96	1.5	7
11	78	96	1	8.5	15	103	84	1.5	6.5
11	82	75	1	10	15	114	96	1.5	9
11	88	108	1	7	15	115	84	1.5	9
11	90	90	1	8	15	124	96	1.5	10
11	100	100	1	8	15	126	80	1.5	10.5
11	101	84	1	9.5	15	134	96	1.5	11.5
12	63	120	1	7	15	156	90	1.5	10
12	64	96	1	8	16	100	96	1	10
12	66	120	1	8	16	106	108	1	13.5
12	67	132	1	6.5	16	120	75	1.5	9.5

longed to from 21 to 45 seconds. Two children who were in the hospital because of surgical conditions had circulation rates of 10 seconds.

The circulation time in normal children as determined by the saccharin test is shorter than the circulation time in adults determined by either the saccharin or the sodium dehydrocholate method. In table 2 are listed the results obtained with various methods for measuring the circulation time.

The increased rate of blood flow in children as determined by the saccharin test is due probably to two factors. In the first place, the actual distance to be traversed from the arm to the tongue in children is less than that in adults. Even if the real rate of circulation were the same in children, the shorter distance would reduce the circulation time between these two points. Secondly, the execution of the test in children induces excitement and an acceleration of the heart rate. There are some reasons for believing that within the limits of cardiac efficiency an increase in the heart rate shortens the circulation time. Winternitz, Deutsch and Bruell considered that there were four factors of influence



on the circulation time: (1) the function of the myocardium, (2) the frequency and rhythm of the heart beat, (3) changes in the blood, and (4) the peripheral variations. In our normal subjects the only variable factor was the pulse rate. None of the other factors existed. All of the observers found a shortened circulation time in exophthalmic goiter with its tachycardia, while in myxedema also the circulatory speed was reduced. We have been able to make observations on a patient with auricular flutter and varying degrees of block. In this patient also the circulation time varied inversely to the ventricular rate.

The suggestion may be raised that the inaccuracy of response in children may account for the fact that their circulation time differs from that of adults. This would be a valid explanation if the circula-

tory time in children were prolonged. Poor cooperation and inaccurate end-point recognition are evidenced not by premature but by delayed responses.

SUMMARY

The circulation time is defined, and its significance is discussed.

With the use of the saccharin method the circulation time was determined in one hundred normal children ranging in age from 8 to 16 years. The technic employed is described.

The average circulation time was 8.6 seconds. The range was from 5 to 13.5 seconds. In eighty-three of one hundred tests the limits were from 6.5 to 10 seconds.

Reasons for the shortened circulation time in children as compared with adults are discussed.

TABLE 2.—*Results Obtained with Various Methods of Measuring the Circulation Time*

Reported by	Method Employed	Circulation Time, Sec.	
		Normal Adults	Normal Children
Weiss, Robb and Blumgart: Am. Heart J. **4**: 664, 1929	Histamine	13-30	
Blumgart and Yens: J. Clin. Investigation **4**: 1, 1927	Radium	14-24	
Hirschsohn and Mandel: Beitr. z. klin. d. Tuberk. **49**: 64, 1922	Calcium chloride	9-15	
Kahler: Wien. Arch. f. inn. Med. **19**: 1, 1930..	Calcium chloride	9-15	
Winternitz, Deutsch and Bruell [2].....	Sodium dehydrocholate	8-14	
Tarr, Oppenheimer and Sager [4].....	Sodium dehydrocholate	10-16	10 (2 cases)
Fishberg Hitzig and King [3].....	Saccharin	9-16	
Authors			6.5-10 (100 cases)

1560 Amsterdam Avenue.

BACILLARY DYSENTERY AS OBSERVED AMONG NORMAL CHILDREN IN HUNTINGTON, WEST VIRGINIA

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INTRODUCTION

The health careers of three hundred normal children are being studied along lines suggested by Dr. Kenneth Blackfan and Dr. Haven Emerson. The episodes of sickness have been observed, their incidence has been noted and an attempt is being made to study their influence on the trend of health, growth and development of the children. Hereditary and environmental characteristics, which appear to be important factors, have been observed, and, so far as possible, their influence on the incidence and the effects of sickness in these children is being studied. Preventive measures, as applied by the individual physician and family, have been employed, their influence has been noted and an attempt is being made to ascertain what has worked and what has not. In considering the results of pediatric supervision as observed in such a group, it is of value to recognize the possibilities and limitations encountered.

Among the most important environmental factors are the presence (and the conditions which influence the presence) of the specific incitants of disease. Of these, especially important are the contagious diseases of childhood, such as tuberculosis, dysentery and malaria. The geographic and climatologic characteristics, the socio-economic status, the prevalence or nonprevalence of specific infectious disease and the presence of special health hazards in the community are but a few of the factors of significance in determining what, when and how illness may occur in a child and be chiefly dependent on environmental endowment rather than on the intrinsic inadequacy of the child. Some of the environmental endowments or liabilities (typhoid, diphtheria, rickets) may be controlled by the individual parent or physician, while others (bacillary dysentery, malaria) require the services of groups or of public health agencies and still others (respiratory infections) remain almost, if not entirely, beyond human control.

Presented at the West Virginia White House Conference on Child Health and Protection, May 29, 1933.

This study has been aided in part by a grant from the De Lamar Institute of Public Health for the purpose of investigating the health careers of normal children.

The high incidence of dysentery observed in this group, occurring in a region in which dysentery is endemic, is evidence of the fact that preventive pediatrics may call for more than the efforts of the individual physician and of cooperative parents. The prevention of dysentery in such a community seems to be even more dependent on the efficiency of the public health agencies and on the social enlightenment of the community than on the activities of each physician or parent. An appraisal of the effectiveness of preventive pediatrics in a community in which dysentery or malaria occurs must take these environmental factors into consideration. It is obviously easy for the physician, parent or public health agency to "prevent" dysentery in a community in which dysentery does not occur but it is not so easy to prevent dysentery in a community in which it is endemic.

No reliable data exist as to the prevalence of bacillary dysentery in this country. The high incidence in the southern part of the United States, especially in the rural sections, is well known to public health workers, but is not so generally appreciated by physicians who have not lived in these sections. The incidence of bacillary dysentery in the mountainous coal mining sections of West Virginia seems to be almost the highest, if not actually the highest, in the United States. The incidence is not so high in the sparsely settled rural district, whether mountainous or not, as it is in those mountainous sections which present a locally congested population, such as is found in the coal mining sections. The recent appearance of bacillary dysentery in Boston, Toronto and Chicago and the interesting clinical and bacteriologic studies carried on in connection with these epidemics should do much to correct the present lack of uniformity in pediatric textbooks and reference books in regard to the true nature of bacillary dysentery as it occurs in children.

For the purpose of definition, bacillary dysentery is considered in this study to be a diarrheal disease characterized clinically by stools containing blood, pus and mucus and brought about by the invasion of the gastro-intestinal tract by the dysentery bacillus. It is commonly referred to as infectious diarrhea, bloody diarrhea, ileocolitis or "flux." In all particulars, this conception of the disease conforms with that given by Holt and Howland [1] in 1926 and by the Committee on Communicable Disease Control of the White House Conference [2] in 1931. Other organisms are credited by some writers as being causative factors in a condition that is clinically similar.

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1. Holt, L. E., and Howland, J.: Disease of Infancy and Childhood, ed. 9, New York, D. Appleton and Company, 1926, p. 295.

2. White House Conference on Child Health and Protection: Section II. Report of Committee on Communicable Disease Control, New York, Century Company, 1931, p. 120.

Paden [3] stated that in West Virginia during a period of five years, from 1926 to 1930, diarrhea was responsible for more than 25 per cent of the deaths occurring among children under 6 years of age; of these, 90.34 per cent occurred among children under 2 years of age, and 64 per cent, among those under 1 year. An analysis of figures supplied by the Bureau of the Census reveals that in West Virginia diarrhea in children under 2 years was characterized by an excessively high mortality rate during the period from 1926 to 1931. During this time, West Virginia maintained a death rate from diarrhea higher than that of any other state in the Union except Arizona and New Mexico. In West Virginia during this period the average annual death rate from diarrhea among children under 2 years was 66.8 per hundred thousand population. In this respect, one county maintained an average annual rate of 127.9, and another county, a rate of 103.3 per hundred thousand population. There is also evidence that in Huntington the period from 1927 to 1931 was a great deal better in this respect than the five year period (1922 to 1926) immediately preceding it (fig. 1). In 1930 the death rate from diarrhea among children under 2 in West Virginia was 70.7 per hundred thousand population. This was the highest rate reported, except in New Mexico and Arizona, and it was nearly twice the next highest rate reported. There is considerable contrast when this figure is compared with the rate of 4.6 for Oregon and that of 5.4 for Washington in the same year, and with the rate of 2.5 for Oregon in 1929. This high rate in West Virginia is an index of the frequency with which dysentery occurs in this state. It furthermore illustrates well an important environmental hazard for the infant and child in this region.

With the foregoing considerations as a background, in a community in which dysentery presents one of the most important medical problems, an attempt has been made to study the incidence and the factors which influence the incidence of dysentery as observed (1) in three hundred normal children living in an urban community who had been under private medical supervision from birth, (2) in one hundred children in the same community who had been under supervision in a baby welfare clinic and (3) in one hundred children living in rural or semiurban centers within a radius of 100 miles (161 kilometers) of the urban area who had been studied and supervised in a general way in private practice. The data from this study are presented in this report.

GROUP ONE

In the health careers of three hundred normal white children, the incidence of dysentery was found to be high. All of the children in this

3. Paden, R. H.: Diarrhea—the Killer, Quart. Bull. West Virginia State Dept. Health **19**:23 (April) 1932.

group were private patients who had been under my supervision from birth and had not come under observation primarily because of ill health.

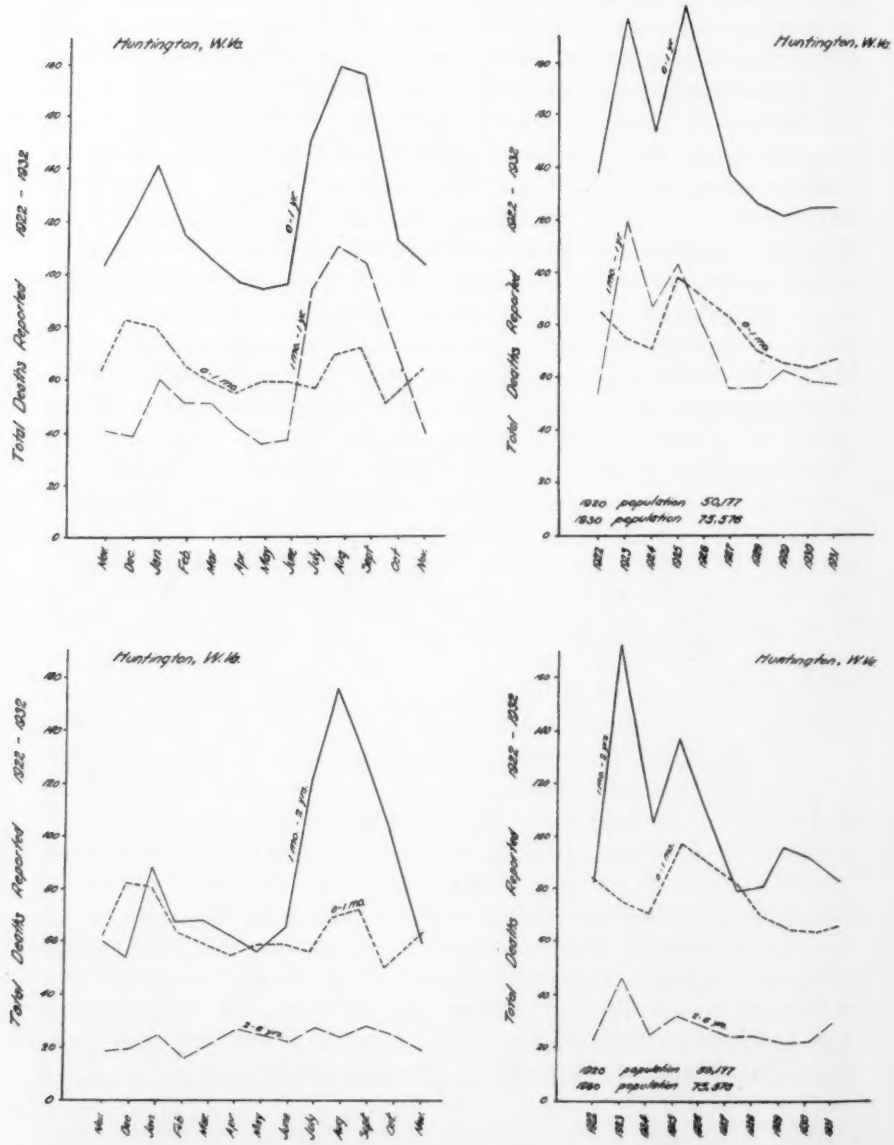

Fig. 1.—Charts showing infant and child deaths in Huntington, W. Va., from 1922 to 1932 by months and by years. Note the advantage of dividing the 0 to 1 year curve into 0 to 1 month and 1 month to 1 year.

They were residents of an urban community (Huntington, W. Va.) in a region in which dysentery is endemic. Of these, 37 per cent had dys-

entery in the first five years of life. This incidence occurred in spite of such preventive measures as the boiling of water and milk, reasonable care in the selection and preparation of food and attempts of individual families to control flies, etc. All of the children were born between 1921 and 1926, and the observations include the period from 1921 through 1927. Between 1921 and 1925 frequent bacteriologic and serologic studies were made, the Flexner bacillus being found in approximately 80 per cent of the cases studied. In the remaining 20 per cent, there may have been other strains, unidentified and atypical, such as those of Sonne, Duval, etc. Shiga's dysentery bacilli and typhoid and paratyphoid bacilli were not found at any time in this study. It was generally possible to demonstrate specific agglutinins in the blood of these patients when their serum was mixed with a suspension of dysentery bacilli.

TABLE 1.—*Distribution and Incidence of Bacillary Dysentery among Three Hundred Children (Group 1)*

Districts Studied*	Number of Children Studied	Number of Children Who Had Dysentery	Percentage Who Had Dysentery	Social Groups of Families of Children Included in Study	Social Groups Prevailing in Districts Studied
1. West End	34	16	47	III, IV, V	II, III
2. Central	47	15	32	II, III	II, III
3. East End	16	10	62	IV, V	III
4. Southside	106	16	15	I, II	I, II
5. Four Pole Park	19	10	52	I	I
6. Pottery	9	5	56	III, IV, V	III
7. C and O Shops	17	10	58	IV, V	III
8. Walnut Hills	16	11	68	IV, V	II, III
9. Highlawn	26	11	43	III, IV, V	II, III
10. Guyandotte	10	7	70	III, IV, V	II, III
Total	300	111	37		

* See map of districts shown in figure 2.

The Flexner bacillus was frequently recovered in cases in which the condition was so mild that the patient did not suffer from fever, malaise, anorexia, etc. In these cases the only findings of importance were blood, pus and mucus in the stools, and these were often present for not more than from one to three days. The patients generally gave characteristic serologic reactions in due time. The importance of the recognition of such mild cases, with their supply of virulent bacilli, can hardly be overemphasized, for they constitute an important unrecognized source and opportunity for the spread of the disease. A control group of children without symptoms was provided in the summers of 1923 and 1924 by another study, which is not reported. In an attempt to study the incidence of Bacillus Welchii in the stools of normal children as compared with those of children with loose stools, the stools of fifty children who were free from symptoms were cultured, and Bacillus dysenteriae and Bacillus typhosus were at no time recovered.

That the mortality rate for dysentery is low in this region may be inferred from the fact that during the period from 1921 to 1931 none of the children whom I had had under supervision from birth died from bacillary dysentery. The generally high death rate for dysentery in this community seems to be indicative of an exceedingly high morbidity rate, and this is found to be true. For children under 5 years of age, the mortality rate from bacillary dysentery in this community has been observed to be low, ranging from 1 to 2 per cent. For infants under 2 years the rate is from 1 to 4 per cent.

If it is assumed that the population consists of five socio-economic groups (group I, highest; group V, lowest), the majority of the three

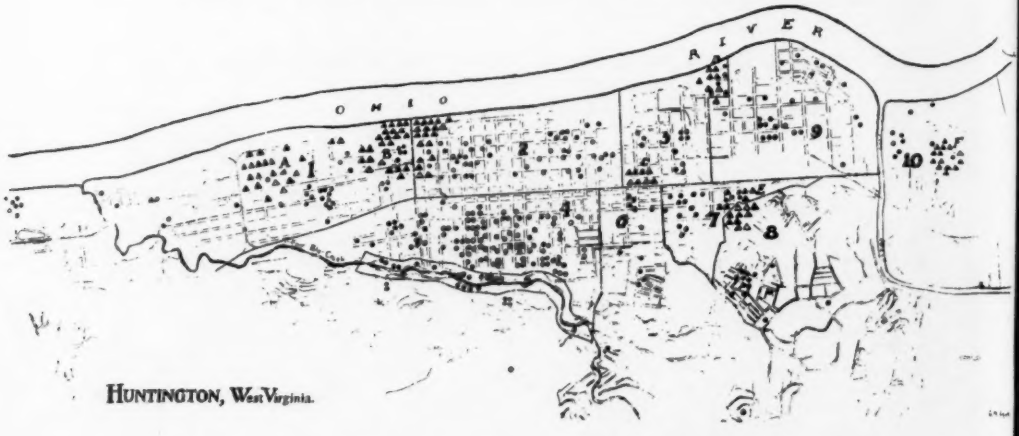

Fig. 2.—Spot map showing distribution and incidence of bacillary dysentery as observed in Huntington, W. Va., from 1921 to 1926 in children during the first five years of life. The open circles represent children seen in private practice who did not have dysentery, and the solid dots represent children seen in private practice who had dysentery. The open triangles represent children seen in the group from the Huntington Baby Welfare Clinic who did not have dysentery, and the solid triangles represent those from the clinic who had dysentery.

hundred children observed in private practice may be said to have belonged to families in groups I, II or III. The parents, as a rule, were intelligent and cooperative, and the homes were such as would be considered physically adequate for the good care of children. Screens were generally used in the doors and windows, garbage was properly protected, and other attempts to control flies were made. It was observed that in certain sections of the city dysentery occurred more frequently than in others. The distribution and incidence of dysentery among these children are indicated in table 1 and also by circles in the spot map shown in figure 2.

GROUP TWO

By way of comparison, a second group consisting of eighty-one white and nineteen colored children from the Huntington Baby Welfare Clinic were studied. They had had medical supervision from shortly after birth, were residents of the same community as those of the former group, were of approximately the same age, were under observation during the same period by the same observer and represent a strictly comparable group. They were all from socio-economic groups IV and V. Dysentery occurred in 72 per cent of these children, and of these fifty-five, or 76 per cent, were white and 17, or 24 per cent, were colored. The incidence among the colored children was higher than that among the white children. Of the white children 68 per cent had dysentery while of the colored children, 89 per cent had dysentery.

TABLE 2.—*Distribution and Incidence of Bacillary Dysentery among One Hundred Children (Group 2)*

District Studied*	Number of Children Studied	Number of Children Who Had Dysentery	Percentage Who Had Dysentery	Social Groups of Families of Children Included in Study	Social Groups Prevailing in Districts Studied
A. West End	20	12	60	IV, V	V
B. Ohio Avenue Johnson Lane	40	34	80.5	V	V
C. Maple Avenue	8	5	62.5	IV	V
D. A and B Streets	8	6	75	V	V
E. C and O Shops	10	6	60	IV, V	V
F. Guyandotte	14	9	64.3	V	V
Total	100	72	72		

* See map of districts shown in figure 2.

(Only 7 per cent of the total population of Huntington is colored so that the racial factor does not contribute greatly to the total high death rate.) The homes of this group were in the main physically inadequate for the suitable care of children. Food was not, as a rule, of the best, as to quality, selection or preparation. Overcrowding was often extreme, and in the very warm months living conditions in some homes were nearly unbearable. There were many small, poorly ventilated houses which were oppressively hot both day and night in summer. Metal roofing, gas lights and the lack of windows added to the oppressiveness of hot, humid weather. Garbage was generally poorly cared for and often openly exposed in close proximity to the living quarters. The mortality rate, which was higher than in the preceding group, was undoubtedly greatly influenced by such unfavorable factors, although it was not so clear to what extent these factors influenced morbidity. Almost invariably flies were present in excessive numbers, and screens and other means for controlling flies were generally lacking. When infection occurred among children in these families, the stools and diapers were rarely

cared for properly. Appropriate cooperation with the medical and nursing advisors was not the rule. Ignorance and indifference apparently contributed greatly to the spread of the disease. It was likewise the lot of these children to be thrown into relatively close proximity to improper devices for the disposal of sewage, open privies, open sewers, sewage-laden creeks, garbage, etc., and likewise to be exposed to more crowded conditions within the home and community and to a greater number of patients with dysentery. Stables are not a source of much difficulty because of their rarity here. The distribution and incidence of dysentery among these children are indicated in table 2 and also by triangles in the spot map shown in figure 2.

GROUP THREE

A third group consisted of one hundred white children, private patients who, while living within a 100 mile (161 kilometer) radius of the city, did not live in the city proper. They were observed at an age and at a time strictly comparable with those for the two former groups. These children, like those of the first group, were taken from socio-economic groups I, II and III and were normal children who did not come under observation primarily because of ill health. The high incidence of dysentery in this group, 52 per cent in the first five years, is probably an index of the frequency with which dysentery occurs in this region, as the group represents a mixture of rural and urban population. The majority of those in this group were the children of physicians, lawyers, engineers, school teachers and other professional people. They were given relatively favorable individual care and protection.

COMMENT

The relative ineffectiveness of individually applicable preventive measures in the protection of the infant against dysentery in such a region is forcibly indicated by these observations. Significant influences commonly present in groups 1 and 3 were: (1) proximity to improper disposal of sewage, (2) proximity to patients with dysentery and (3) the influence of heavy infestation by flies. In both groups the children were unusually favored as to socio-economic grouping, had intelligent, cooperative parents and were in some measure protected by the preventive measures usually advocated in private practice. In spite of this, the incidence of dysentery was high, and higher in those districts where disposal of sewage was least sanitary and where flies and patients with dysentery were most numerous.

In addition to the factors which seemed of significance in groups 1 and 3, in group 2 were observed also the deterimental effects of (1) poor socio-economic status (with accompanying ignorance), (2) over-

crowding, (3) poor and insanitary surroundings and (4) lack of proper individual hygienic care, etc.

By far the most significant factors common to all of the groups were the presence of patients with dysentery, heavy infestation by flies and improper disposal of sewage.

Not infrequently in the urban area studied, the appearance of cases of dysentery among colored tenants (social group V) living on an alley at the rear of a lot would be followed by the appearance of cases in the homes of well-to-do white people (social group I) living on a fashionable avenue at the front of the same lot.

While the incidence of dysentery was considerably greater in warm weather, the condition was observed regularly, although with less frequency in cold weather. Similarly, flies were to be observed in the homes of some of these patients at all times of the year. It may be of interest to mention a prominent lunchroom located in the city which for years has been infested by flies more heavily in winter than in summer. It is open day and night the year round and has a warm, moist, fly-favorable atmosphere during the winter. Some of the homes observed present conditions equally favorable to the propagation and protection of flies throughout the winter, and I have, in more than one instance, observed cases of fly-borne dysentery which were contracted during zero or near-zero weather. In January 1923, when the weather was severely cold, I exposed plates of Teague's medium (on the surface of which had been placed a small amount of sterile molasses) in one home where there were two children with dysentery. Flies were seen to visit these plates, and from them a considerable number of colonies of the Flexner bacillus were recovered. Of course, in this home the journey of the fly from an infected diaper to the culture medium was short and easy of accomplishment.

In a community in which dysentery bacilli are commonly encountered, prolonged, warm, humid, atmospheric conditions facilitate the spread of the disease, probably by favoring bacterial existence outside the human host and by favoring the reproduction of flies through facilitating larvation and pupation. Probably atmospheric conditions exert their greatest influence on the incidence of dysentery in this way, rather than by reducing the specific resistance of the child (a view greatly favored at one time). While the influence of atmospheric conditions on incidence is brought about indirectly by action on the child's environment, the mortality is undoubtedly increased directly because of the adverse effects of these conditions on the sick child.

Of great importance in the rural areas would seem to be the unusual geographic and topographic characteristics of the communities under observation. In all of the rural areas included in this study there are hills and small mountains with precipitous sides and with small streams

coursing through the valleys. On the banks of these creeks and in valleys with bottoms ranging from only a few hundred feet to a few hundred yards in width, are congregated over 90 per cent of the population of the entire county or community. This congestion of population approaches closely that of the urban industrial community. A valley with a bottom 400 yards (0.36 kilometer) wide is seldom seen, and one with a width of 800 yards (0.73 kilometer) is indeed rare. While the bottom-lands are heavily populated, the slopes and tops of the hills are practically uninhabited. There are no table-lands and no flat hill-tops, such as would favor agriculture or the heavier population of the hills. Therefore, in close proximity along the creeks is found the bulk of the population and into the creeks comes all of the refuse from the nearby homes and from those on the hillsides. Open, insanitary privies are numerous. The distance from a privy to the creek is often only a few feet, and frequently a privy is built directly out over the creek. Proximity to streams heavily laden with sewage, together with an almost urban overcrowding and congestion of population, seems to present a unique and characteristic problem of control of communicable diseases. In these communities, dysentery is present during every month of the year. The peak is reached in August and September (not June and July, as is the case farther south) and the minimum is reached in January and February.

By way of illustration, it may be well to describe a demonstration which was carried on by Dr. David Littlejohn of the State Department of Public Health. In most coal mining camps, the operators' resident staff, the superintendents and the engineering and business staffs take their meals in a club-house, which, as a rule, has the most favorable situation in the camp. It is generally the custom, after washing and drying the dishes and silverware following a meal, to set the table for the next meal, placing the dishes right side up. On one occasion, Dr. Littlejohn visited one of these camps and after the noon meal (fresh white linen and clean white dishes having in the meantime been placed on the table) he placed a copious amount of a heavy red dye in the privy, which, incidentally, was a "three holer" about 60 feet (18 meters) from the dining table. By the time for the evening meal an abundance of little red fly tracks on the linen and dishes spoke eloquently of the rôle that the fly plays in the transmission of fecal material to eating utensils and food in these camps. The operators were impressed by this demonstration, and the camp now has proper sanitation. Unfortunately, adjoining camps are still insanitary, and they present a discouraging handicap to those camps which strive for proper sanitation and maximum protection.

The seasonal curves (fig. 1) showing deaths among infants in Huntington (Cabell county) give an index of the problem. Neighboring mining counties also present remarkable seasonal curves (fig. 3).

In this study it has not been possible to place the blame on a poor water supply. While in Huntington, between 1921 and 1926, the drink-

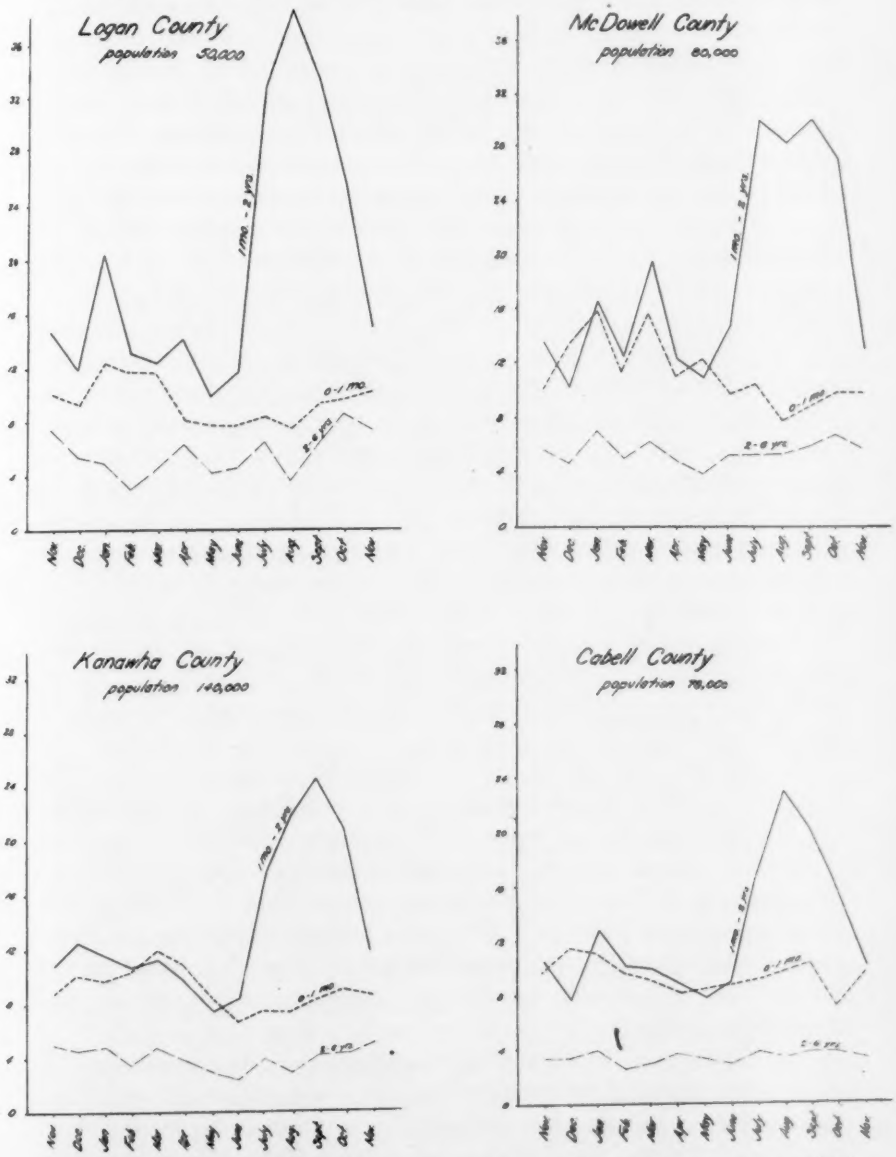

Fig. 3.—Charts showing the average number of deaths reported per hundred thousand population by months in four counties of West Virginia for the decade from 1923 to 1932 for the age groups 0 to 1 month, 1 month to 2 years and 2 to 6 years.

ing water for children was boiled in almost all instances, this was probably an unnecessary procedure, as the municipal water supply

was at that time and has been continuously since of excellent quality as regards freedom from typhoid and dysentery bacilli.

It has been possible to attach very little blame to the milk supply for the reason that much of the milk was pasteurized and in almost all cases it was also properly boiled.

In 1921 I felt that dysentery in this section was most likely due to poor milk and water supplies. While either may in specific instances be an important contributory factor, the possibility that either was of major causal importance in this community is untenable in the light of these studies and my subsequent observations. This is important, because it should tend to focus attention on sanitation as the fundamental procedure for the prevention of dysentery in this community.

The influence of climate on the incidence of dysentery was also carefully considered in this study, and observations were carried out during a greater part of the period, and have since been continued. The following factors were found to be of importance: (1) a warm mean temperature with relatively hot days and nights, (2) high humidity accompanying a relatively high mean temperature and (3) a long duration of the so-called "hot humid spells." Without going into the technic of the study more extensively, suffice it to say that the relative humidity was determined in the conventional manner by means of wet bulb and dry bulb readings, a sling psychrometer and psychrometric tables. Mechanical devices were used at times but when so used were tested with such frequency and regularity as to assure their accuracy. Other climatic data were received from the United States weather observer in Huntington.

The observations on the effects of the atmospheric factors on the incidence of dysentery may be summarized as follows: A continuously hot, humid season was invariably accompanied by an increased incidence of dysentery. Cool summers, dry summers and seasons characterized by short periods of "hot spells" and by cool nights were accompanied by a lower incidence of dysentery. It seems reasonable to assume that these atmospheric influences were active not so much by their effect on the human host as indirectly by favoring maximum propagation of and infestation by flies.

The summers of 1923 and 1925 were characterized by unusually high mean temperatures, high relative humidities and prolonged periods of hot weather. Similarly, flies were particularly numerous during these two years. Relative humidities ranging from 50 to 80 per cent were recorded almost generally during the hot weather. The incidence of dysentery at this time was high, the severity of the cases was unusually great, and the mortality rate was increased proportionately.

The summers of 1922, 1926 and 1927 were characterized by less extreme conditions of heat and humidity. While the temperatures were

high, relative humidities of from 20 to 50 per cent were more common than those above 50 per cent. The periods of hot weather were not so remarkably prolonged as they were in 1923 and 1925. Flies were less numerous, and the incidence and severity of dysentery were diminished. The manner of estimating the degree of the infestation by flies was simply that of careful observation, and from a scientific point of view was not acceptable. However, until a better means of estimation is available, it seems permissible to consider the remarkable differences noted in this connection and to include them with the other observations.

SUMMARY

Some idea of the frequency with which dysentery has been encountered among four hundred children in an urban community in which dysentery is endemic is presented. From 15 to 80 per cent of the children of the city of Huntington had bacillary dysentery at some time during the first five years of life. Cases were observed more frequently in those sections of the city which were characterized by the presence of heavy infestation by flies, by improper disposal of sewage and by the presence of patients with dysentery. Cases developed in spite of the usual preventive measures, such as the boiling of all milk and water, the careful selection of food, the attempts of individual families to combat flies, etc.

The summers that were characterized by prolonged periods of high temperatures (from 80 to 100 F.) when accompanied by high relative humidities (from 50 to 80 per cent) were also characterized by a maximum infestation by flies and a high incidence of dysentery (1923, 1925). Summers that were characterized by equally high temperatures, but by lower relative humidities (from 20 to 50 per cent) and shorter periods of extremely hot, humid weather, were characterized by a relatively light infestation by flies and a low incidence of dysentery (1922, 1926, 1927). As far as the influence of atmospheric conditions on the incidence of dysentery is concerned, the prolongation of the hot, humid weather and of the elevation of the relative humidity seemed to have more influence than the height of the temperature.

Overcrowding, poor socio-economic status and the features which usually accompany such conditions were important factors which tended to increase the incidence of dysentery among the children cared for by the Baby Welfare Clinic. The children living in rural or semiurban areas presented a higher incidence than the children of a comparable class living in the urban area. The peculiar topographic characteristics of parts of the rural region, together with the unique congregation of population along small streams in an urban form of congestion, with improper protection of sewage and with the presence of carriers of

and patients with dysentery, all created a situation which tremendously favored the spread of dysentery.

Typhoid can to some extent be held in check by the administration of vaccine, and this has proved of great value in the checking of epidemics, even in the absence of good sanitation, in the rural communities here under consideration. Unfortunately, there is no similar individually applicable agent for the prevention of dysentery. The indifference of the leaders in the community, their lack of appreciation of the value of the proper disposal of sewage and of the control of flies, their failure to regard dysentery as a communicable disease of economic importance and their objections to the alleged "expense" of proper preventive measures have been important obstacles against forward progress in the control of bacillary dysentery in these areas. Unfortunately, these dysentery-ridden rural areas act as foci of infection, feeding the adjacent rural and urban areas. Therefore, milk and water for the infant should certainly be boiled, and food should be carefully selected and properly prepared. Infestation by flies should be held to a minimum, for flies are probably the vectors of major importance in the spread of dysentery in these sections. Droughts hinder and wet seasons favor heavy infestation by flies. With atmospheric temperatures at the usual summer levels (70 to 105 F.) wet seasons with relative humidities of from 60 to 90 per cent tend greatly to favor heavy infestation by flies, but with the same atmospheric temperatures dry seasons and droughts with relative humidities of from 20 to 40 per cent tend greatly to reduce or prevent heavy infestation by flies. The institution and maintenance of safe disposal of sewage, the isolation of patients with dysentery, the eradication of breeding places for flies, etc., are problems for the community and the state and only indirectly may be considered as problems for the individual. The physician can do little more than assist in a program of public health education. This education, however, is essential to the eradication of dysentery in the communities here studied. In this region neither the most expert physician nor the most alert and cooperative parent can with certainty protect the child from dysentery.

CONCLUSION

In the community studied, from 15 to 80 per cent of the children observed had dysentery before the end of their fifth year. Among private patients, the incidence was 37 per cent (urban) and 52 per cent (semi-urban). In the Baby Welfare Clinic group, the incidence was 72 per cent (urban).

The presence in the neighborhood of patients with dysentery, the improper disposal of sewage and infestation by flies seem to be the factors most active in determining the prevalence of dysentery.

In a community in which it is endemic, bacillary dysentery appears as an environmental endowment which may affect the welfare of the children of that community adversely. It cannot be controlled by preventive measures that are individually applicable, and its prevention in such a community is truly a public health problem. As such, it constitutes a real limitation in pediatric practice. An appraisal of the possible accomplishments of preventive measures in a community must take into consideration this important environmental handicap.

ADDENDUM

The period from Feb. 15 to Oct. 15, 1934, was one of extreme drought and of generally high atmospheric temperature in Huntington and the neighboring counties of West Virginia. During the third week of August there was a little rainfall, but even then the precipitation was greatly below the normal for that period of the year. The summer atmosphere temperatures were abnormally elevated for unusually long periods of time. The dry bulb temperatures of from 90 to 100 F. were frequent and at times sustained and persistent, and temperatures of 105 F. and over were not infrequent. The relative humidities during the day from May 1 to August 15 were regularly observed to be below 40 per cent and on several occasions were actually as low as from 18 to 20 per cent. This is to be compared with the usual summer day-time relative humidities of from 50 to 90 per cent. The relative humidities at night were of course somewhat higher, but during the summer there was one period of ten days when the humidity did not exceed 30 per cent day or night and the temperature during the day was regularly abnormally high, reaching from 95 to 100 F. So dry, in fact, were the spring and the summer that heavy foundations that had been "settled" for years began to settle again and to crack. (Foundation engineers state that this condition is a regular accompaniment of extreme conditions of drought.) Throughout the entire summer the lawns, fairways and parks were almost entirely without grass and what little grass there was was a barren brown. During the latter part of August a few days of rain interrupted the drought temporarily and day-time relative humidities of from 50 to 60 per cent were noted for five consecutive days, only to be followed by another period of drought and of low relative humidities. For the period of unusual asmospheric findings, the following observations were made:

1. Flies were so scarce that window screens were not a necessity in my home until after August 20. Then for a little more than a week there was some "fly nuisance," following which flies were again scarce for another four or six weeks, returning thereafter in their usual number. Lightning bugs, which are usually observed in great numbers, were remarkable by their scarcity. Mosquitoes, which are generally quite a nuisance locally, were so greatly reduced in numbers during the period of drought that they were observed with remarkable rarity.

2. The hot dry temperatures of from 90 to 100 F. were generally not as enervating as the usual summer season temperatures of from 80 to 85 F. with their usually accompanying relatively high humidities.

3. People perspired visibly only to a remarkably slight degree, considering the height of the atmospheric temperatures. Particularly was this true as observed during exercise on the golf course.

4. Small streams in the parks, on the outskirts of the city and in the adjoining counties were largely dried up.

5. Cases of bacillary dysentery were observed with relative rarity from February 1 to September 15, the incidence being undoubtedly the lowest ever observed in the community.

6. If any deaths occurred from bacillary dysentery from February 1 to September 15, they were a rarity.

7. From April 15 to August 15 the Huntington Baby Clinic had practically no cases of bacillary dysentery or of infectious diarrhea, in fact, less than five cases, but the usual number would have been from eighty to one hundred and twenty for this period.

8. During the first eight months of 1934 deaths from diarrheal diseases among children under 2 years of age dropped to 37.6 per cent below the lowest previous record for the same period of the year. The installation before midsummer of approximately 25,000 sanitary privies in the state by the FERA and the State and Federal Public Health Service may have had a large influence on the incidence of disease.

9. The period of rain with increased relative humidities in the latter part of August was promptly followed not only by a short period of appreciable "fly nuisance" but almost as promptly by the sudden outbreak of cases of bacillary dysentery, as observed at the Huntington Baby Clinic and in private practice. (It is of interest to note that a neighboring part of southeastern Ohio, a section geographically similar to southwestern West Virginia, had practically normal summer atmospheric temperature and humidities, with considerable rainfall, good crops, green pastures, lawns and fairways, and that the incidence of bacillary dysentery was high from April 1 to August 15).

10. During the first eight months of 1934 it was possible to trace practically every case of bacillary dysentery in Huntington directly to the fact that the child had been camping or living along the banks of one of the rural streams which was low but which had not been entirely dried up. In such situations the fly nuisance was observed to be at its usual excessive degree.

From observations such as those just cited one cannot escape the belief that it is not the height of the atmospheric temperature alone but rather the high temperature in relation to the high relative humidity that constitutes the "complex" which is the actual determining atmospheric influence in the incidence of bacillary dysentery and of other forms of fly-borne infectious diarrhea. It is logical to believe that the atmospheric "humidity-temperature complex" is effective quite as much through favoring or hindering the development of flies as through favoring or endangering the existence of bacteria outside the human host.

While I have made similar observations locally in lesser degree in former seasons of extreme atmospheric conditions, the intensity and persistence of the aridity in the drought of the spring and summer of 1934 were accompanied by such a low infestation by flies and such a low incidence of cases of bacillary dysentery that the obvious relation seems to be most convincing.

EFFECT OF SCARLET FEVER ON IMMUNITY TO DIPHTHERIA AS DETERMINED BY THE SCHICK TEST

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The study reported on here, which extended over a period of four years, was concerned with observations on the effect of scarlet fever on immunity to diphtheria as determined by the Schick test in 219 hospitalized patients. The incentive to the study arose when one of us observed that clinical diphtheria developed in a patient who was convalescing from scarlet fever, although on admission the Schick reaction was reported to be negative. The question immediately presented itself as to whether this was due to faulty technic or to weak toxin or whether there might be a loss of immunity to diphtheria following an attack of scarlet fever. The possibility of weak toxin was quickly ruled out not only because fresh potent toxin is received at frequent intervals from the bureau of laboratories of the department of health but more so because other patients gave a positive Schick reaction at the same time to toxin from the same batch.

METHOD AND MATERIAL

A Schick test with a control was performed as a routine on every patient with scarlet fever admitted to the Willard Parker Hospital, the only exceptions being patients who had had diphtheria antitoxin administered prior to or on admission. If the patient was in the early stage of the infection, had not had any kind of inoculation within the preceding three months and was reported as having given a negative reaction to the Schick test, on the third day following admission another Schick test with a control was performed by one of us; if the reaction was still negative, the patient was again retested on the twenty-seventh, twenty-eighth or twenty-ninth day of the illness and sometimes repeatedly tested if he remained in the hospital for a longer period. The interdiction against patients who had had inoculations within three months ruled out the possibility that any of those tested might possess passive immunity. Results were read on the fourth day.

The average number of days of illness on admission was three and three-eighths. The ages of the patients are given in the following tabulation.

Age, Years	No. of Patients
1- 5	32
5-10	60
10-20	34
20-30	31
30-40	10
Over 40	2

From the Scarlet Fever Service of the Willard Parker Hospital.

RESULTS

Effect of Scarlet Fever on Immunity—Of the 219 patients who gave negative reactions to the Schick test on the first and third days of hospitalization, 7 showed a positive reading on the thirtieth day of hospitalization, and 1 on the thirty-fourth day, making a total of 8 patients, or 3.65 per cent, whose reactions became positive. The age and sex of these patients are given in the following tabulation.

Age, Years	Sex
2	F.
3	F.
7	F.
8	F.
10	F.
13	M.
21	F.
29	M.

Effect of Complications on Loss of Immunity to Diphtheria.—Of the 219 patients, 43, or 19.5 per cent, had complications. All of the 43 patients gave negative reactions to the Schick test on the first, third and thirtieth days in the hospital.

Effect of Administration of Antitoxin on Loss of Immunity to Diphtheria.—Of the 219 patients studied, 119 were given scarlet fever antitoxin on the day of admission. Five thousand units was administered intramuscularly in each case. In 2 cases the dose was repeated on the second and third days, respectively.

Eight patients lost their immunity to diphtheria as determined by the Schick test—6, or 6 per cent, of the group of 100 patients who did not receive antitoxin, and 2, or 1.6 per cent, of the group of 119 who received antitoxin. Although this was very likely a coincidence, it appears that the administration of scarlet fever antitoxin apparently lessened the patients' chances of losing their immunity to diphtheria.

COMMENT

It is odd that every patient who lost his immunity had had uncomplicated scarlet fever that was relatively mild or of moderate severity. The age of the patient did not prove to be a deciding factor. Offhand, one would think that if there is to be a loss in immunity the patients suffering from a severer infection are more likely to be affected. Yet there were 2 cases in the series which were extremely severe but in which the patient, even after one hundred and fifteen days, gave negative reactions to repeated Schick tests. One immediately draws the conclusion that the technic was at fault. It may be added that when the test is performed by an expert in the routine way, that is, when three hun-

dred tests are performed per hour, there is an error of 1 or 2 per cent.[1] However, an error of over 3 per cent would be rather too high for an experienced person to make especially when the tests were performed on such a selected group of patients.

Although far from conclusive, the results indicate that immunity to diphtheria or, in other words, the concentration of diphtheria antitoxin in the human body varies. There is no reason why it should not vary, for immunity proves to be only a relative quantitative factor. For example, certain infections produce or leave immunity, but the immunity does not always prove to be permanent, as the infections are known to recur. A recurrence is thus an indication that there has been a decrease of protective substances in the body. This may be more readily understood when one considers that the concentration of antitoxin or of any immune body varies with the individual. In the case of diphtheria antitoxin, some persons have a concentration of antitoxin in their serums as high as 60 units per cubic centimeter,[2] and perhaps more, whereas other persons have barely enough to neutralize the one-fortieth minimal lethal dose which is introduced in the Schick test, while still others are nearly devoid of demonstrable antitoxin. When there is a high concentration of diphtheria antitoxin an appreciable amount of antitoxin can be lost without the patient's being susceptible to diphtheria, but when the concentration is low the loss of an appreciable amount of antitoxin renders a former negative Schick reaction positive. For example, Neill and his associates[3] observed a variation of 35 units of diphtheria antitoxin in the blood of a normal person within fourteen days. Perkins and his co-workers[4] noted that the antitoxin concentration in a small group of adolescent children reached a peak in August and September and a low level in late winter and early spring, while in a similar group of adults there were two peaks within a year, which not only reached much higher levels but occurred in an inverse synchronism with the values for the adolescent group. There appeared to be no apparent difference according to whether or not the patients had previously received toxin-antitoxin immunization. In the adult group, there was a person who gave a negative reaction to the Schick test on two occasions following toxin-antitoxin immunization and who after each negative test lapsed into a state of positive reaction, with almost com-

1. Park, W. H.: Personal communication.

2. Sugg, J. Y., and Neill, J. M.: Loss of Immune Substances from the Body: II. Diphtheria Antitoxin in Human Saliva, J. Immunol. **20**:463 (June) 1931.

3. Neill, J. M.; Gaspari, E.; Mosley, R. A., and Sugg, J. Y.: Loss of Immune Substances from the Body: III. Diphtheria Antitoxin in Human Sweat, J. Immunol. **21**:101 (Aug.) 1931.

4. Perkins, R. G.; Heeren, R. H.; Megail, E., and Grossman, A. B.: Seasonal Variation of Diphtheria Antitoxin Content of the Blood of Adults and Adolescents, Am. J. Hyg. **10**:13 (July) 1929.

plete absence of titrable antitoxin. On the other hand, Fitzgerald,[5] working with a small group, observed that if the antitoxin concentration was 1 unit or more per cubic centimeter there was a fluctuation as high as 1.5 unit per cubic centimeter but that if the antitoxin concentration was less than 0.1 unit per cubic centimeter of serum there was no marked variation in the concentration over a period of two years. He also stated that he had not seen any one lose his immunity to diphtheria. Martin and others [6] noted that persons may have their own levels of antitoxin content, and that there is a limit to which this level can be permanently raised. In several of their cases in which the antitoxin concentration had been raised to many times its original value by the use of anatoxin, the concentration dwindled in the course of a month to a lower level, though it remained above the original level; when it was again raised by additional doses, it fell even more rapidly to approximately the same level. A seasonal variation in a Schick test was found by Tubiasz [7] who noticed that of a large group of persons from 7 to 13 years of age 48 per cent gave positive reactions to the Schick test in January, while only 21 per cent gave positive reactions to this test during the following September. Nélis,[8] on the contrary, did not find a variation of this sort. An almost incredible oscillation of the reaction to the Schick test after forced military marches was reported by Zlatogoroff and Kostereff.[9] For example, in one group of 60 patients 12 gave positive reactions to the Schick test five days before the march; immediately after the march there were 42 positive reactions, and ten days later there were only 21 positive reactions. In another group of 82 patients there were 17 positive reactions to the Schick test five days before the march and 58 immediately afterward. Park,[10] who stated the belief that a negative reaction to this test may render one immune to diphtheria indefinitely, nevertheless stated that the slight fluctuation of antitoxin which occurs in every immune person may cause certain patients with borderline cases to give at times a positive reaction and at other times a negative reaction.

5. Fitzgerald, J. G.: The Question of Variation in Diphtheria Antitoxin Content of the Blood of Adults, Tr. Roy. Soc. Canada **20**:355 (May) 1926; Acta med. Scandinav. **70**:396, 1929.

6. Martin, L.; Loiseau, G., and Laffaille, A.: L'immunisation antidiphtérique par l'anatoxine chez l'homme. Applications à la prophylaxie de la diphtérie (décembre 1923—mai 1928), Ann. Inst. Pasteur **42**:1010 (Sept.) 1928.

7. Tubiasz, S.: Les fluctuations saisonnières de la réaction de Schick chez les enfants polonais, Bull. Office internat. d'hyg. pub. **24**:2000 (Dec.) 1932.

8. Nélis, P.: Au sujet des variations saisonnières de la réaction de Schick, Compt. rend. Soc. de biol. **112**:546 (Feb. 17) 1933.

9. Zlatogoroff, S. I., and Kostereff, S. A.: Oscillations des réactions de Schick et de Dick sous l'influence de marches forcées, Compt. rend. Soc. de biol. **106**:96 (Jan. 23) 1931.

10. Park, W. H.: Does a Negative Schick Test Indicate Present and Future Security from Diphtheria? Arch. Pediat. **38**:329 (June) 1921.

Nukada and Kako [11] demonstrated that when guinea-pigs and rabbits were immunized against the Bordet-Gengou bacillus or the gonococcus, ten days later an increased resistance developed against diphtheria toxin; this was shown by the fact that following the administration of lethal doses of toxin, these animals lived longer than did the controls. This difference was not marked but definite, and is more interesting when compared with the results obtained in experiments on guinea-pigs and rabbits, which were immunized against the streptococcus and which in contrast showed less resistance to the diphtheria toxin than did the controls. Madsen and Schmidt [12] found that guinea-pigs were more susceptible to diphtheria toxin in the winter than in the summer. After testing 66 college students, Panina and Kostereff [13] noticed that 12 per cent more of them gave positive reactions to the Schick test five months after receiving typhoid and paratyphoid inoculations than before receiving the inoculations. They obtained about the same results in a group of 45 students who were retested only a week later following the inoculations.

The observations of many investigators lend proof not only that there are definite fluctuations of diphtheria antitoxin in the blood of normal persons, but that the fluctuations can be influenced to some extent by outside factors. How much or how much more fluctuation, if any, there may be in patients with scarlet fever remains to be seen.

Park and Zingher [14] were the first to draw attention to the fact that 57 per cent of persons who have had scarlet fever give positive Schick reactions as compared with 24 per cent of persons of the same age (from 2 to 8 years) who have not had scarlet fever. Kolmer and Moshage [15] deduced from their studies with the Schick test that there was an increased susceptibility to diphtheria in persons suffering from scarlet fever. They found that in children with scarlet fever passive immunity following the injection of diphtheria antitoxin was of shorter duration than that induced among approximately normal children in that

11. Nukada, S., and Kako, Y.: Ueber die Schwankungen der Resistenz gegen Diphtherietoxin nach Immunisierung mit Heterobakterien, Klin. Wchnschr. **8:** 2143 (Nov. 12) 1929.

12. Madsen, T., and Schmidt, S.: Seasonal Variation in Susceptibility of Laboratory Animals to Toxin, Acta Soc. med. fenn. duodecim (ser. A, art. 4) **15:**1 (Sept. 6) 1932.

13. Panina, A. I., and Kostereff, S. A.: Ismenie reakzii Schicka i Dicka u v zroslych pod vlijaniem privivki divakzinoi protiv tipha i paratipha B, Voj. med. j. **2:**517 (July 3) 1931.

14. Park, W. H., and Zingher, A.: Diphtheria Immunity—Natural, Active and Passive: Its Determination by the Schick Test, Am. J. Pub. Health **6:**431 (May) 1916.

15. Kolmer, J. A., and Moshage, E. L.: A Note on the Occurrence of Pseudoreactions on the Skin, J. A. M. A. **65:**144 (July 10) 1915.

10 per cent of the former were susceptible within ten days after receiving antitoxin. Whether this was due to accelerated elimination of the horse serum antitoxin during the acute stage of scarlet fever or to other causes they were unable to state. In a later paper [16] Kolmer and Moshage acknowledge that they were misled by the pseudoreactions to the Schick test which occur in no small number of people, but they did not report whether or not this accounted entirely for their findings. Zingher,[17] moreover, observed a much higher percentage of positive reactions to the Schick test not only in patients with scarlet fever but in those who had measles or poliomyelitis. To account for this abnormally high percentage, he offered two possible causes: (1) There may be a destruction of antitoxin during these diseases, and (2) susceptibility to one of the less contagious diseases indicates that the person is more likely to be susceptible to other contagious and infectious diseases. When he stated "less contagious" he must have had only scarlet fever and poliomyelitis in mind, for with the exception of chickenpox it is hard to find any disease which is more highly contagious than measles. Hull [18] performed Schick tests on a group of 120 adults and 10 children. Of 107 patients who had no history of scarlet fever, 52 per cent gave positive reactions to the Schick test, as contrasted with 87 per cent of 23 patients who had had scarlet fever.

The only previously reported study of the Schick test made during both the acute febrile and the convalescent stage of scarlet fever is that of Eddy and Mitchell,[19] which appeared in November 1930, during the second year of our investigation. They tested 186 patients and noted that the reaction of 1 of them had changed from negative to positive. They did not consider that this finding was important and concluded that there was no change in the reaction of the skin to diphtheria toxin during the acute febrile and the convalescent stage of scarlet fever. Their results are interesting, although they are not entirely comparable to ours in view of the fact that at the onset of the observation over half of their patients gave positive reactions, while all of our patients gave negative reactions. Moreover, they considered a reaction positive only when it was 1 cm. or more in diameter, whereas according to Schick [20] a reaction is positive when the diameter exceeds 5 mm.

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16. Kolmer, J. A., and Moshage, E. L.: The Schick Toxin Reaction for Immunity in Diphtheria, Am. J. Dis. Child. **9**:189 (March) 1915.

17. Zingher, A.: The Schick Test in Poliomyelitis, Scarlet Fever, Measles, and in Normal Children: Its Bearing on the Question of Natural Immunity, Am. J. Dis. Child. **13**:247 (March) 1917.

18. Hull, T. G.: The Schick Test and Scarlet Fever, J. Lab. & Clin. Med. **11**: 260 (Dec.) 1925.

19. Eddy, B., and Mitchell, A. G.: Studies in Immunity: III. The Effect of Diseases Other Than Diphtheria on the Schick Test, Am. J. Dis. Child. **40**:985 (Nov.) 1930.

20. Schick, B.: Personal communication.

Where the antitoxin goes when it decreases in amount remains debatable. Some of it has been shown by Sugg and others to be excreted in the saliva and in smaller amounts also in the urine [21] and sweat. These routes, however, account for only a part of the loss.

This study shows that a small percentage of persons lost their immunity to diphtheria following an attack of scarlet fever, but it also shows what is just as or even more striking that the overwhelming majority retained their immunity. Whether the persons who had a reversal of the reaction to the Schick test would spontaneously have reverted to a negative reaction after a time is questionable. It is rather unfortunate that they were advised to undergo inoculation with toxin-antitoxin or toxoid immediately following their discharge from the hospital. Furthermore, these observations would have been more enlightening if the serum had been titrated for the presence of antitoxin when the tests were being performed. The fact that in a number of patients the reaction to the Schick test became positive is almost insignificant; nevertheless, it is significant enough to sound a warning that "once immune" does not necessarily mean "always immune," and that it seems advisable to repeat the Schick test during the convalescence of every patient with scarlet fever and perhaps after any prolonged or severe illness.

CONCLUSIONS

1. Of 219 hospitalized patients with scarlet fever, 8 lost their immunity to diphtheria as determined by the Schick test.

2. The presence of complications, the severity of the infection and the age of the patient had no effect on the loss of immunity to diphtheria.

3. Of the group of patients to whom antitoxin had been administered, 1.6 per cent lost their immunity to diphtheria as compared with 6 per cent of the group of patients to whom no antitoxin was administered.

4. Every patient with scarlet fever should be given a Schick test during his convalescence; and until it has been demonstrated that a positive reaction to the Schick test may revert spontaneously to a negative one following an attack of scarlet fever, the patient should be immunized if the reading is found to be positive.

1245 Madison Avenue.

33 East Sixty-First Street.

21. Neill, J. M.; Gaspari, E. L., and Mosley, R. A.: Loss of Immune Substances from the Body: I. Diphtheria Antitoxin in Human Urines, J. Immunol. **20**:347 (May) 1931.

INTESTINAL FLORA IN NEW-BORN INFANTS

WITH A DESCRIPTION OF A NEW PATHOGENIC ANAEROBE, BACILLUS DIFFICILIS

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AND
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Following our first article on the bacterial flora of first passage specimens of meconium from fifty new-born infants [1] we studied the daily microbial changes in the feces of ten normal breast-fed infants up to the tenth day, when they left the hospital.

HISTORICAL REVIEW

The early invasion of the intestinal tracts of new-born infants by bacteria, either ascending or descending, often within ten hours after birth and before feeding, first observed microscopically by Breslau [2] in 1866, was confirmed by Billroth [3] in 1874 and by Nothnagel [4] in 1881. Using iodine as a stain, Nothnagel assumed to identify Saccharomyces ellipsoideus, Bacillus subtilis and the so-called clostridium of Prazmowski, which he regarded as identical with Bacillus amylobacter of Trecul and van Tieghem and the "vibrion septique" of Pasteur; but we feel that even now, with greatly improved methods of staining, identification of any of these is impossible.

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This investigation was supported in part by grants from the Commonwealth Fund of New York and the Child Research Council of Denver.

1. Hall, I. C., and O'Toole, E.: Bacterial Flora of First Specimens of Meconium Passed by Fifty New-Born Infants, Am. J. Dis. Child. **47**:1279 (June) 1934.

2. Breslau: Ueber Entstehung und Bedeutung der Darmgase bei neugeborenen Kindern, Monatschr. f. Geburtsh. u. Frauenkr. **28**:1, 1866.

3. Billroth, T.: Untersuchungen über die Vegetationsformen von Coccabacteria septica und den Antheil welchen sie an der Entstehung und Verbreitung der accidentellen Wundkrankheiten haben, Dissert., Berlin, 1874; cited by Woodward, J. J.: The Medical and Surgical History of the War of the Rebellion, Washington, D. C., Government Printing Office, 1879, vol. 1, pt. 2, p. 869.

4. Nothnagel, H.: Die normal in den menschlichen Darmentleerungen vorkommenden niedersten (pflanzlichen) Organismen, Ztschr. f. klin. Med. **3**:275, 1881.

Nothnagel was severely criticized by Bienstock,[5] in 1884, for his failure to use the "modern" staining and cultural methods of Koch. These methods enabled Bienstock to make beautifully colored plates of fecal bacilli with red spores (central, terminal or free), but one wonders how Bienstock avoided discovering Bacterium coli, for if he ever had it in pure culture his record fails to prove it. Perhaps if he had known of Gram's method of staining, which was reported in the same year, he might have discovered that bacterium.

However, it was Escherich[6] who in 1885 utilized Gram's method of staining and Koch's method for the isolation of bacteria on solid mediums and thus laid the real basis for modern conception of normal intestinal bacteriology. Escherich showed that in some cases, even when bacteria were not demonstrable microscopically, their presence could be shown culturally as early as the fourth hour, that the first invaders were *tetradencocci* and *kettencocci*, that while the flora of the first day was usually simple, that of succeeding days was more complex, often containing in addition to Bact. coli and Bacterium aerogenes (which he first described), B. subtilis, other sporulating bacilli and yeasts, and that this variable flora gave way about the fourth day on the replacement of the dark tarry meconium by the yellow mucoid acid milk stool, to a flora in which slender, granular staining, gram-positive, nonsporulating rods greatly predominated. However, when cultures on agar plates were made from milk stools, gram-positive bacteria rarely appeared, but only the gram-negative Bact. coli or Bact. aerogenes. This was for Escherich an apparently insoluble enigma which he attempted to explain by assuming that the staining reactions of these organisms were altered in the intestinal tract. Schmidt,[7] under the guidance of Escherich, attempted to explain this by the action of fat in the feces, but cultures made on butter agar and butter gelatin were still gram-negative.

The tinctorial discrepancy between the bacteria stained directly in milk stools and those in aerobic cultures finally found its true explanation in the isolation of Bacillus bifidus by Tissier[8] in 1899, and of

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5. Bienstock, B.: Ueber die Bakterien der Fäces, Ztschr. f. klin. Med. **8**:1, 1884.

6. Escherich, T.: Die Darmbakterien des Säuglings und des Neugeborenen, Fortschr. d. Med. **3**:515, 1885; Die Darmbakterien des Säuglings und ihre Beziehung zur Physiologie der Verdauung, Dissert., Stuttgart, 1886; Ueber Darmbakterien im allgemeinen und diejenigen der Säuglinge im besonderen, Centralbl. f. Bakt. (Abt. 1) **1**:705, 1887.

7. Schmidt, A.: Zur Kenntnis der Bakterien der Säuglingsfaeces, Wien. klin. Wchnschr. **5**:643, 1892.

8. Tissier, H.: La réaction chromophile d'Escherich et le Bacterium coli, Compt. rend. Soc. de biol. **51**:943, 1899; Repartition des microbes dans l'intestin du nourrisson, Ann. Inst. Pasteur **19**:109, 1905.

Bacillus acidophilus by Moro [9] in 1900. The dependence of these aciduric species, now assigned to the genus Lactobacillus, on an increased hydrogen ion concentration of the contents of the lower part of the bowel due to fermentation of lactose or dextrin and their important relation to healthy intestinal conditions at all ages have received much emphasis in the subsequent work of Cahn,[10] Sittler,[11] Logan,[12] Adam,[13] Rettger and Cheplin,[14] Brown and Bosworth,[15] Cruickshank,[16] Cruickshank and Berry,[17] Kopeloff [18] and many others. Naujoks [19] showed that a majority of pregnant women harbor B. acidophilus in the vaginal secretions, so practically every infant acquires it at birth, an arrangement exquisitely implicative of teleologic significance.

NEW WORK

Our present interest centers in the unstable period of the first few days after birth.

Our methods were similar to those already described: [1] the collection of feces on sterile diapers, suspension in sterile water, microscopic examination of slides stained by methylene blue and by Gram's method, and primary cultures for aerobic bacteria on blood agar and eosin methylene blue lactose agar plates, and for anaerobic bacilli in dextrose broth constricted tubes and deep iron brain medium with isolation and

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9. Moro, E.: Ueber die nach Gram färbbaren Bacillen des Säuglingsstuhles, Wien. klin. Wchnschr. **13**:114, 1900.

10. Cahn: Ueber die nach Gram färbbaren Bacillen des Säuglingsstuhles, Centralbl. f. Bakt. (Abt. 1) **30**:721, 1901.

11. Sittler, P.: Beiträge zur Bakteriologie des Säuglingsdarmes, Centralbl. f. Bakt. (Abt. 1) **47**:145, 1908; Die wichtigsten Bakterientypen der Darmflora beim Säugling, Dissert., Würzburg, 1909.

12. Logan, W. R.: The Intestinal Flora of Infants and Young Children, J. Path. & Bact. **18**:527, 1914.

13. Adam, A.: Ueber Darmbakterien, Ztschr. f. Kinderh. **29**:59, 65 and 306, 1921; **30**:265, 1921; **31**:331, 1922; **33**:308, 1922.

14. Rettger, L., and Cheplin, H.: Transformation of the Intestinal Flora, New Haven, Conn., Yale University Press, 1921.

15. Brown, E. W., and Bosworth, A. W.: A Bacteriologic Study of Feces and Food of Normal Babies Receiving Breast Milk, Am. J. Dis. Child. **23**:243 (March) 1922.

16. Cruickshank, R.: Bacillus Bifidus; Its Characters and Isolation from the Intestines of Infants, J. Hyg. **24**:241, 1925.

17. Cruickshank, R., and Berry, D. W.: A Study of Bacillus Acidophilus in Human Feces, Brit. M. J. **2**:944, 1924.

18. Kopeloff, N.: Lactobacillus Acidophilus, Baltimore, Williams & Wilkins Company, 1926.

19. Naujoks, H.: Das Vorkommen des Bacillus acidophilus bei Schwangeren und Gebärenden und sein zeitlicher und örtlicher Uebergang auf den Neugeborenen, Centralbl. f. Bakt. (Abt. 1) **86**:581, 1921.

identification according to the methods of Hall.[20] Exhaustive efforts were made to isolate every possible micro-organism except L. acidophilus and L. bifidus, which have received so much attention that the special efforts required for their cultivation seemed unjustified for our present purpose; their presence with a few exceptions was therefore judged purely from the microscopic observations.

RESULTS

For the sake of brevity the results are condensed in the table, which shows the days on which the specimens were collected in relation to the observations recorded. Unfortunately, some specimens were lost, the night nurses forgetting to save them; the days on which no specimens were obtainable are shown. Sixty-three specimens were examined, of which thirty-one were black or brown, i. e., meconial, while thirty-two were typical yellow milk stools.

Sterile Stools.—Six infants passed sterile stools on the first day, but no sterile stools were passed after that. From three of these infants, second specimens were obtained on the same day, and in each specimen bacteria were evident both microscopically and culturally. In addition, three other infants passed specimens of meconium during the first twenty-four hours of life in which bacteria were demonstrated culturally but not microscopically.

Species of Micrococcus.—Various white species of Micrococcus appeared during the first or second days in seven cases. Micrococcus albus, Micrococcus candidus and Micrococcus epidermidis, as defined by Hucker,[21] were found most frequently. It was interesting to note the repeated isolation of a given species from consecutive specimens from the same infant.

Species of Streptococcus.—Nonhemolytic streptococci appeared in the stools of all but one infant at some time during the ten day period. All were isolated and identified according to Holman's classification.[22] Streptococcus mitis occurred in specimens from nine of the infants; Streptococcus faecalis occurred in seven, and in the stools of five babies Str. mitis appeared day after day. Another interesting observation was that of a nonhemolytic, bile nonsoluble, inulin-fermenting streptococcus which closely resembled the Streptococcus cardio-arthritidis of Small [23];

20. Hall, I. C.: The Study of Obligately Anaerobic Bacteria, in Society of American Bacteriologists, Manual of Methods for Pure Culture Study of Bacteria, ed. 2, Baltimore, Williams & Wilkins Company, 1932, Leaflet 3.

21. Hucker, G. J.: The Species of the Genus Micrococcus, Centralbl. f. Bakt. (Abt. 1) **64**:481, 1925.

22. Holman, W. L.: The Classification of Streptococci, J. M. Research **34**:377, 1916.

23. Small, J. C.: Observations Bearing on the Specificity of Streptococcus Cardio-Arthritidis in Rheumatic Fever and Sydenham's Chorea, Am. J. M. Sc. **175**:638, 1928.

Observation	Days After Birth on Which Specimens Were Collected										Percentage of Cases
	Infant 1	Infant 2	Infant 3	Infant 4	Infant 5	Infant 6	Infant 7	Infant 8	Infant 9	Infant 10	
Sterile specimens	.....	1	1	1	.....	1	1	.....	.....	1	60
Positive microscopically	2,3,4,5,6,7	1,3,7	3,4,10	2,4,8,9,10	2,3,4,6,7,8	1,2,3,5,6,7,8,9	1,3,4,5,6	2,3,4,5	2,6,9	2,3,4,6,7,8	
M. albus	1, 7	.....	.....	.....	7	5,6,7,8,9	.....	1,9	1	6	60
M. candidus	6	.....	.....	.....	4,6,7	.....	1,3,4,5	1	.....	3	50
M. epidermidis	.....	9	.....	4	.....	1,2,3	1,6	1,2	2,6,9	2,7,8	70
M. ureae	.....	.....	.....	.....	.....	.....	.....	3,4,5	.....	.....	10
M. varians	.....	7	.....	2	.....	.....	.....	.....	6	.....	30
M. roseus	1	.....	.....	.....	.....	.....	.....	.....	.....	.....	10
Str. faecalis	1	7,9	10	4	.....	.....	6	2,4,9	.....	6,7,8	70
Str. mitis	2,3,4,5	1	4	8,9,10	2,3,4,5,6,8	2,3,5,6,7,8,9	1,3,4,6	3	.....	2,3	90
Str. cardio-arthritidis	.....	.....	.....	.....	.....	5,6	.....	.....	.....	4	20
Bact. coli	5,6,7	1,3,7,9	3,4,10	8,9,10	2,3,5,6,7,8	.....	3,4,5,6	1,2,3,4,5,9	9	3,4,6,7	90
Bact. paracoli	.....	1	.....	.....	.....	.....	.....	.....	.....	.....	10
Bact. aerogenes	2,3,4,5,6,7	3,7,9	3,4,10	8,9,10	2,3	.....	3,4,5,6	2	.....	4,6,7,8	80
Bact. paratyphosum B	.....	.....	3	.....	.....	.....	.....	.....	.....	.....	10
Kopfchenbacterien	.....	3	10	2,4,8,9	2,3,4	2,3,5,6,7	.....	.....	.....	3,4,6,7	60
B. difficilis	.....	.....	.....	10	.....	2,3,5,6,7	.....	2,3,4,5	.....	3,4,7	40
Hay bacillus	.....	.....	.....	.....	.....	5	1,3,4	9	.....	8	40
Yellow stools	3,4,5,6,7	3,7,9	10	2,4,8,9,10	3,4,6,7,8	6,7,8,9	6	4,5,9	6,9	6,7,8	100
L. acidophilus and L. bifidus*	2,3,4,5,6,7	3,7	3,4,10	2,4,8,9,10	2,3,4,6,7,8	5,6,7,8,9	4,5,6	3,4,5,9	6,9	3,4,6,7,8	60
Specimens not available	8,9,10	2,4,5,6,8,10	2,5,6,7,8,9	3,5,6,7	9,10	4,10	2,7,8,9,10	6,7,8,10	3,4,5,7,8,10	5,9,10	100

* The lactobacilli were seen microscopically, but were not recovered in pure culture.

it occurred on the fourth day in the specimens from one infant and on the fifth and sixth days in specimens from another.

Bacterium Coli and Bacterium Aerogenes.—Bact. coli appeared in nine specimens on the first, second or third days, and once established persisted in subsequent specimens. Bact. aerogenes likewise appeared in eight specimens, but in two of these only once or twice. Bacterium paracoli was found once in a first day specimen, and Bacterium paratyphosum B appeared once in a third day specimen.

Lactobacillus Bifidus and Lactobacillus Acidophilus.—Yellow milk stools were first seen once on the second day, three times on the third day, once on the fourth day, four times on the sixth day and once on the tenth day, but in the last instance no specimens were examined between the fourth and tenth days. In three cases microscopic examination of the first yellow stools revealed slender, gram-positive, beaded or club-shaped rods in palisade arrangement which we interpreted as L. acidophilus or L. bifidus; in seven cases these organisms were seen one or two days preceding the appearance of the first yellow stool. In no case did we fail to demonstrate them in large numbers in every specimen after their first appearance. They unquestionably constitute the predominating species of the yellow milk stool, as has often been pointed out. Only occasionally does one see L. bifidus as a branched organism in the feces, but we have often seen it in mixed cultures, and after the most meticulous effort one of us (E. O'T.) has isolated a few pure strains.

Hay Bacilli.—Large gram-positive aerobic sporulating hay bacilli were isolated in four cases, but in only one did they reappear; in the other three they seemed accidental. The anaerobic habitat of the human bowel is unfavorable to their lodgment as an intrinsic part of the intestinal flora.

Anaerobic Bacilli.—We repeatedly recovered two species of anaerobic bacilli.

The first of these closely resembled the *Kopfchenbacterien* of Escherich.[6] These organisms have been observed in the stools of newborn infants by several investigators, but since their proper classification and nomenclature are still under discussion and will be the subject of a separate contribution, we shall here content ourselves with the original vulgar designation.[24] The *Kopfchenbacterien,* as we found them, were slender, slightly motile, gram-variable, obligately anaerobic bacilli with oval terminal spores, fermenting, with the production of acid and gas, dextrose, levulose, galactose, maltose, lactose, sucrose, raffinose, dextrin,

24. Since this article was written, Hall and Snyder (J. Bact. **28**:181, 1934) have indicated the probable identity of the *Kopfchenbacterien* of the feces of infants with Rodella's Bacillus III and Bacillus paraputrificus (Bienstock).

starch, amygdalin and salicin, not fermenting xylose, inulin, mannitol and glycerol, and practically lacking in proteolytic action, as indicated by their failure to liquefy coagulated blood serum, casein or gelatin, and by their nonproduction of sulphuretted hydrogen or indol. They were nonpathogenic for guinea-pigs and rabbits.

Kopfchenbacterien were seen in most of the stools from which they were isolated, and, as shown in the table, they appeared in specimens from six of the ten infants at some time during the ten day period of observation—in three on the second, in two on the third and in one on the tenth day. In four infants they were found repeatedly in from three to five specimens and in two only once, and in every instance they disappeared from the stools before the last specimens were obtained, a valid reason for which has been offered by Adam [13] in his observation that these organisms require for their best growth a neutral or alkaline reaction, while the lactobacilli require an acid reaction. The *Kopfchenbacterien* are thus definitely germs of the period of transition from nearly neutral meconium to the typical acid milk stool. Yet they occur occasionally in the feces of older children and adults and are a not infrequent finding at autopsies on adults.

A NEW PATHOGENIC ANAEROBIC BACILLUS FROM STOOLS OF INFANTS

The second obligately anaerobic bacillus was an actively motile, heavy-bodied rod with elongate subterminal or nearly terminal spores of about the same diameter as the rods (figs. 1 and 2). This species was isolated in pure culture from thirteen specimens obtained from four infants: from one on the second, third, fifth, sixth and seventh days, from another on the second, third, fourth and fifth days, from another on the third, fourth and seventh days and from one on the tenth day. In three of these infants the bacillus was associated with the *Kopfchenbacterien*; it appeared and apparently disappeared at about the same time and under the same conditions. When both were present each complicated the isolation of the other, but this anaerobe was more difficult to isolate than the *Kopfchenbacterien* and much more difficult to study, owing to its slower growth and less striking physiologic properties.

From the thirteen strains isolated, four (one from each infant) were studied in detail at 37 C. and with essentially identical results. In deep brain medium containing iron wire the production of gas and turbidity in twenty-four hours was slowly followed after a week or ten days by moderate blackening, indicating the formation of a small amount of sulphuretted hydrogen. Neither gelatin nor Löffler's blood serum were liquefied in fifteen days. Milk was a poor medium, generally

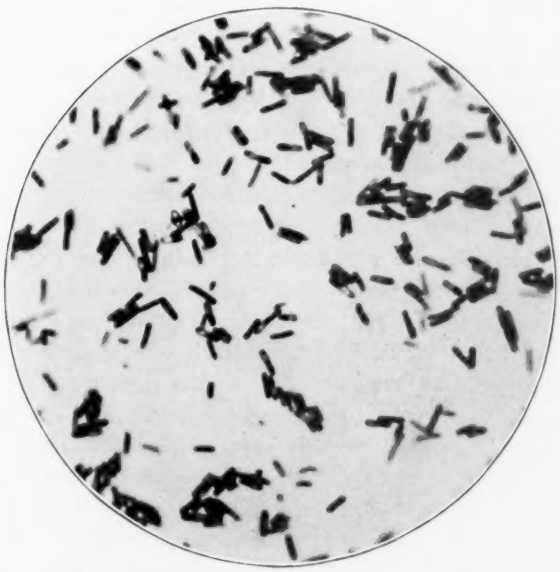

Fig. 1.—Bacillus difficilis (new species). A smear from a forty-eight hour blood agar slant under alkaline pyrogallol stained by Gram's method to show vegetative rods and spores; × 500.

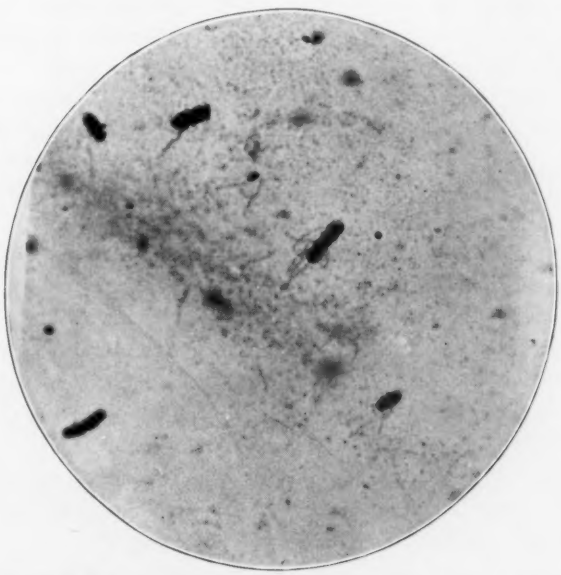

Fig. 2.—Bacillus difficilis (new species). A smear from a twenty-four hour blood agar slant under alkaline pyrogallol stained by Bailey's method (Bailey: Science **52**:95, 1930) to show flagella; × 1,000.

showing no change or only a trace of gas on prolonged incubation. With suitable dilutions, well separated colonies generally appeared in deep agar on the second day of incubation; at first they were minute flat opaque disks, later becoming lobulate and reaching a diameter of 1 mm. in about three days. No free gas was formed in this medium, even when the tubes were heavily seeded.

Well separated colonies on blood agar slants under alkaline pyrogallol were irregular in form, flat and nonhemolytic.

Considerable difficulty was encountered in testing the fermentation reactions. Hiss serum water sugar mediums, which sufficed without a special seal for the *Kopfchenbacterien,* required specially prepared [25] seals for growth with the new bacillus and failed to indicate the fermentation reactions satisfactorily, probably because of the weak acid and the high buffering effect of the serum proteins. Broth mediums in constricted tubes were likewise unsatisfactory, perhaps because the organism grew too slowly to prevent the gradual return of inhibiting oxygen past the marble seals. It was therefore necessary to use broth fermentation mediums covered with the special seals; in these a turbid growth generally occurred over night, with gas collecting under the seals by the second day. Reaction changes were tested by the addition of bromthymol blue to a few drops of culture removed by a Pasteur pipet to a white porcelain spot plate. Both acid and gas were produced in dextrose, levulose, mannitol, salicin and xylose, but only traces of gas and no acid were produced in galactose, maltose, saccharose, lactose, raffinose, inulin and glycerol.

We were surprised to find the new bacillus highly pathogenic for guinea-pigs and rabbits.

Each of the thirteen strains was tested at least once in guinea-pigs, and the four strains selected for special study were tested many times. Dextrose broth cultures forty-eight hours old were inoculated subcutaneously in doses of 2 cc. in most instances. The guinea-pigs ranged in weight from 175 to 350 Gm., averaging 219 Gm. It may be of some significance that the tests were conducted with cultures of organisms which had been isolated as long as three years previously.

Within from ten to sixteen hours following inoculation all guinea-pigs showed from moderate to marked edema spreading over the belly and breast from the site of inoculation. They refused to eat, were in evident pain, particularly when handled, and would sit humped up with the hair bristling.

Some of the animals earlier in the series showed marked tympanites, but we failed to confirm the observation of this symptom in the later series, and we suspect the presence in the earlier guinea-pigs of an accidental secondary infection or possibly avitaminosis, the effects of which were augmented by the injections.

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25. The seals were a mixture of equal parts of petrolatum and paraffin used to exclude the air from cultures of anaerobic bacteria.

Early in the observations it was noticed that certain guinea-pigs when handled would suddenly jump excitedly, stiffen all four legs posteriorly, throw the head back and collapse suddenly into cataleptic convulsions with breathing suspended, the pulse barely perceptible and the eyelids tightly closed. Some animals died during such convulsions, but the majority began to revive after from thirty to sixty seconds, as shown by tremors of the limbs, labored breathing and opening of the eyes. In a few minutes they would again be able to sit up and even to run around nervously.

After seeing this peculiar phenomenon we watched every animal closely during the day and often late into the night. A tabulation showed that convulsions were observed at least once in twelve of twenty-two guinea-pigs and in most of the twelve more than once. Superficially the spasms resembled those of tetanus, except that the extensor muscles were more markedly affected and the attacks were more transient than those of tetanus.

Handling did not invariably initiate convulsions, and some animals went into convulsions without handling. Certain animals grew restless, the skin seemed to itch or be painful and they whined and turned half way around in a nervous jump; such animals would almost always have a convulsion on the slightest provocation, as handling, lifting of the cage or slamming of a door.

After partial recovery from an attack, further stimulus generally failed to initiate another until after the lapse of about an hour. Every attack was preceded and followed by periods of intense nervousness with tremors. Some animals were seen to have as many as five attacks during the first or second day before dying. If they failed to die during the first forty-eight hours after inoculation it seemed harder to stimulate the onset of a convulsion by artificial means.

Sixteen of the twenty-two guinea-pigs in this series died as follows: four the first day, four the second, two the third, one the fourth, two the fifth, one the seventh, one the eighth, and one the ninth; six recovered.

Later we learned that veal infusion broth cultures gave more striking results than did dextrose broth. For example, 2 cc. of a three day veal infusion broth culture, 4,307, was inoculated subcutaneously in guinea-pig 1,762, weighing 150 Gm. On the following day there was moderate subcutaneous edema. Convulsions with coma occurred promptly on handling. The respiration and heart beat were barely perceptible for five minutes, after which the animal slowly began to recover and was able to sit up. At the end of one hour its back was scratched gently, whereupon it immediately went into another cataleptic convulsion, but not complete coma. Temporary recovery occurred in about one minute, and further handling failed to elicit additional response. In fifteen

minutes, however, it collapsed almost completely, but again revived and did not die until a spontaneous convulsion occurred more than an hour later.

The postmortem lesions were always striking, the most constant macroscopic characteristic being marked subcutaneous edema with or without congestion but with no emphysema or lysis. Smears from the subcutaneous site of inoculation in one animal that died in four hours showed numerous gram-positive rods, but no spores and no leukocytes. In all others, phagocytic leukocytes were found, but few if any free bacteria. Heart blood cultures always gave negative results; there was no evidence of septicemia.

The visceral lesions were inconstant. In some, the lungs were congested, in others not. The gallbladders in some animals were full, in others empty. The suprarenal glands were slightly congested in some cases, in others not. No macroscopic lesions were seen in the livers or spleens, and there was no enlargement of the latter.

The foregoing observations on guinea-pigs naturally suggested the production of a soluble exotoxin, and its presence in broth culture filtrates of all four cultures was readily proved.

Guinea-pig 1,741, weighing 160 Gm., was inoculated intraperitoneally with 2 cc. of the sterile Mandler filrtate of a forty-eight hour old dextrose broth culture, 4,111. The guinea-pig was found dead on the following day. There was no subcutaneous edema or congestion. The heart was normal, but the lungs and suprarenal glands were congested and there were several cubic centimeters of free fluid in the peritoneal cavity. The gallbladder was empty.

Further observations were made with a sterile 3 day old veal infusion broth culture filtrate of strain 4,307; 1 cc. was inoculated subcutaneously into guinea-pig 1,621, weighing 150 Gm., at 5 p. m. On the following day at 9 a. m. there was moderate subcutaneous edema. When picked up the animal was rigid, and trembled. Placed on its feet it fell on its side in violent convulsions, from which it gradually and apparently almost completely recovered in about five minutes. At 12:30 p. m. it was again picked up, and again it went at once into violent convulsions on its side; the body was rigid with tremors, the breathing was imperceptible and the heart beat rapidly and unsteadily; but gradual recovery occurred in about five minutes. At 2 p. m. there was another convulsion without handling which terminated in death. The heart continued to beat for several minutes after respiration ceased. A peculiar phenomenon was the squeezing out of a milky secretion from the eyes during the terminal convulsion. We have seen this in other animals of the series; the secretion apparently contained large numbers of droplets of fat.

At autopsy there was moderate subcutaneous edema, in which neither body cells nor bacteria could be recognized microscopically. The lungs and suprarenal glands were congested and the gallbladder was full; otherwise there were no macroscopic lesions in any of the organs, including the brain.

Guinea-pig 1,628, weighing 150 Gm., was inoculated subcutaneously with 1 cc. of the same filtrate diluted 1:10 in 85 per cent solution of sodium chloride. On the following day there was moderate edema. No convulsions were elicited by handling, but the animal was found dead the next day. A few pus cells were

recognized in the subcutaneous edema fluid. The lungs and suprarenal glands were congested, but there were no other macroscopic lesions. The gallbladder was full.

Guinea-pig 1,630, weighing 150 Gm., was inoculated subcutaneously with 1 cc. of this filtrate diluted 1 : 100. At 11 a. m. the following day it was picked up; at once it exhibited a convulsion lasting about one minute from which it quickly recovered and ran around. At 11 : 35 it had a spontaneous convulsion and cried; at 11 : 44 it was dead. The autopsy observations were similar to those on the preceding animal.

Guinea-pig 1,769, weighing 200 Gm., was inoculated with 1 cc. of the filtrate diluted 1 : 1,000. No symptoms appeared in this animal.

The toxicity of the filtrate therefore lay between 100 and 1,000 minimum lethal doses per cubic centimeter. Boiling for one minute completely destroyed the toxicity.

Rabbits were also found to be highly susceptible. Subcutaneous inoculation of either cultures or filtrates in 2 cc. doses killed small rabbits (400 Gm.) in from two to six days. Edema developed, but no convulsions were seen in the rabbits. The postmortem lesions were similar to those in the guinea-pigs. Heart blood cultures were always negative.

Intravenous injections likewise resulted fatally, with marked congestion and edema of the lungs. A rabbit, weighing 3,200 Gm., given an injection of 2 cc. of a three day old dextrose broth culture (4,307) died in less than sixteen hours.

Further study is under way to determine the properties of this new bacterial neurotoxin, and rabbits are being immunized both with whole cultures and with filtrates to test its antigenic properties.

We have carefully searched the literature for a previous description of this second anaerobe, but so far without success; it is therefore named Bacillus difficilis because of the unusual difficulty which was encountered in its isolation and study.

COMMENT

We have thus confirmed anew the early occurrence of a variety of bacteria in the feces of new-born infants, including two species of anaerobic bacilli, one of which appears not to have been described previously. As a result of our limited observations we believe that these anaerobes disappear with the stabilization of the milk stool flora and return on weaning, but proof of this will require further examinations during and after the nursing period.

We do not regard the initial bacterial invasion of the intestinal tract as entirely accidental, but rather as inevitable, owing to exposure to the flora of the vaginal and intestinal tracts of the mother during labor, later to that of her nipples and perhaps of her germ-laden mouth, and to that of the bath water and other obvious sources of bacteria. The air, so often mentioned by early writers, is perhaps the least important source of bacteria for the new-born.

Whether there is reaction on the part of new-born babies to their first contact with bacteria is unknown, but Bonar [26] suggested that the appearance of occult blood in about 29 per cent of the stools of new-born infants is not physiologic and may be due to intense hyperemia of the intestine caused in part by bacterial action. The initial diarrhea sometimes encountered in new-born infants might also be explained in the same manner. We suspect that convulsions in babies may sometimes be due to the absorption of the toxin of B. difficilis from the intestinal tract where there may have been, for one reason or another, a failure in the development of the normal milk stool flora and an abnormal persistence of the organism. This, of course, presents an interesting problem for the future.

SUMMARY

An intensive study of sixty-three specimens of meconium and feces secured from ten new-born infants during the first ten days of life showed that while seven passed sterile specimens on the first day, bacteria were present in all specimens by the second day. At least five genera and eighteen species were represented, comprising M. albus, M. candidus, M. epidermidis, Micrococcus ureae, Micrococcus varians, Micrococcus roseus, Str. faecalis, Str. mitis, Str. cardio-arthritidis, Bact. coli, Bact. paracoli, Bact. aerogenes, Bact. paratyphosum B, *Kopfchenbakterien,* B. difficilis (new species), Hay bacillus, L. acidophilus and L. bifidus.

Among these, M. albus, M. candidus, M. epidermidis, Str. faecalis, Str. mitis, Bact. coli, Bact. aerogenes, *Kopfchenbacterien,* and the lactobacilli appeared at some time during the first ten days in more than 50 per cent of the infants studied and may be regarded as the most common early bacterial invaders of the intestinal tract of man.

The repeated finding of a new species of pathogenic anaerobe, B. difficilis, in the specimens of four of ten infants during the first ten days of life suggests that it may be interesting to study the reported appearance of occult blood in the feces of the new-born, the initial diarrhea sometimes observed in new-born infants and selected cases of convulsions of unexplained origin in infants, with special reference to the occurrence of this organism in the feces.

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26. Bonar, B. E.: Blood in the Stools of the New-Born, Am. J. Dis. Child. **36**:725 (Oct.) 1928.

Case Reports

EOSINOPHILIA

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Hypereosinophilia is found in many diseases. Kilduffe [1] lists the conditions as follows: myelogenous leukemia, bronchial asthma, scarlatina, various skin diseases, helminthic infestations, gonorrhea, active tuberculosis and convalescence from pyogenic infections. The occurrence of well marked eosinophilia in cases of carcinoma of the stomach,[2] breast [3] and other organs has been reported. In the cases of carcinoma the percentage of eosinophils ranged from 5 to 48.

Persistent and unexplained eosinophilia has been described by several authors. The term "familial" or "constitutional" is used to indicate eosinophilia of unexplained origin in several members of a family. In 1911 Klinkert [4] reported a family of six with eosinophil counts varying from 7 to 15 per cent. Gaugain [5] reported a mother and three children with counts of 9, 10, 14 and 15 per cent. Armand-Delille, Hurst and Sorapure [6] reported a family in which a boy of 8 years had an eosinophilia of between 51 and 62 per cent, with a leukocytosis that at times reached 29,600. Three sisters and one brother had eosinophil counts of 14, 27, 27 and 21 per cent, respectively, while the father had one of 7 per cent. Two other children in the family had normal blood counts. A complete study was made of this family, and all the usual causes of eosinophilia were carefully excluded. Stewart [7] reported four families with eosinophilia. In one of these families, the father, the mother, two daughters, the father's brother and the mother's sister and two brothers had eosinophil counts of 17, 20, 32, 28, 15, 15, 22 and 15 per cent. There was no family relationship between the father and mother before marriage. One of the two daughters had a florid type of tuberculosis.

From the Milwaukee Children's Hospital.

1. Kilduffe, R. A.: The Clinical Interpretation of Blood Examinations, Philadelphia, Lea & Febiger, 1931, p. 257.

2. Weiss, E.: J. Lab. & Clin. Med. **11**:733, 1926.

3. Donati, M.: Gior. d. r. Accad. di med. di Torino **4**:405, 1901.

4. Klinkert, D.: Berl. klin. Wchnschr. **48**:938, 1911.

5. Gaugain, cited by Bezançon, F., and Moreau, R.: Ann. de méd. **2**:85, 1914.

6. Armand-Delille, P. E; Hurst, A. F., and Sorapure, V. E.: Familial Eosinophilia, Guy's Hosp. Rep. **80**:248, 1930.

7. Stewart, S. G.: Familial Eosinophilia, Am. J. M. Sc. **185**:21 (Jan.) 1933.

Tuberculosis has been reported as a cause of eosinophilia. Grass and Simmert [8] recorded eosinophilia as an index of allergy in tuberculosis. Belloni [9] described the increase in eosinophils in infantile tuberculosis, and Brumlik and Sikl [10] and others reported cases of eosinophilia associated with tuberculosis of lymph nodes.

In the other three families reported by Stewart the eosinophilia was persistent and no cause could be found except in one member, a man 38 years old with asthma of five years' duration. Dalla Palma [11] reported a woman of 34 years with persistent unexplained eosinophilia. The leukocyte count ranged from 14,800 to 32,000 with from 43 to 75 per cent eosinophils. Splenic therapy was tried. The administration of solutions of spleen and extracts of spleen (200 Gm. of spleen daily) as well as irradiation of the splenic area resulted in a stimulation rather than an inhibition of the eosinophilia. Mayr and Moncorps [12] produced hypo-eosinophilia by the injection of methyl-alcoholic extract of spleen in amounts equivalent to from 8 to 40 Gm. of spleen. This form of treatment was used in various skin diseases and in the prevention of anaphylactic reactions.

Dermatoneuromyositis has been reported by Sluczewski [13] and others (Hepp, Fahr and Unverricht). Sluczewski's patient had pains in the arms and legs and an inflammatory condition of the skin followed by atrophy of muscles. This condition was accompanied by eosinophilia. Sheldon [14] reported a similar clinical picture without eosinophilia occurring in a boy of 9 years. Rosenthal and Hoffman [15] reported a case of dermatoneuromyositis with resultant scleroderma in a woman 19 years old. They did not mention eosinophilia.

Under the title "Eosinophilic Leukemia," Bass [16] reported an 8 year old Puerto Rican boy who had a persistent leukocytosis ranging between 26,000 and 47,000 with an eosinophilia of from 32 to 46 per cent. A roentgenogram of the chest showed irregular mottling in both lungs. None of the usual causes of eosinophilia were discovered. The basal metabolic rate was markedly elevated. In this article Bass reviewed

8. Grass, H., and Simmert, H. U.: Klin. Wchnschr. **10**:1457, 1931.

9. Belloni, G.: Clin. pediat. **12**:371, 1930.

10. Brumlik, J., and Sikl, H.: Folia haemat. **43**:1, 1930.

11. dalla Palma, M.: Familial Eosinophilia, Policlinico (sez. med.) **38**:605 (Dec.) 1931.

12. Mayr, J. K., and Moncorps, C.: München. med. Wchnschr. **73**:1777, 1926.

13. Sluczewski, A.: Case Report of Dermatoneuromyositis, Dermat. Ztschr. **61**:390, 1931.

14. Sheldon, J. H., and Sheldon, W.: Dermatomyositis, Proc. Roy. Soc. Med. **25**:413 (Feb.) 1932.

15. Rosenthal, C., and Hoffman, H.: A Case of Dermatoneuromyositis with Resultant Scleroderma, Klin. Wchnschr. **3**:115 (Jan. 15) 1924.

16. Bass, M. H.: Eosinophilic Leukemia, Am. J. Dis. Child. **41**:1394 (June) 1931.

several recorded cases, including those reported by Hay and Evans.[17] He drew attention to the fact that the cases cited had many features in common. The white cell count was persistently high. The percentage of eosinophils was high—higher than found in other diseases. The eosinophils were of the mature type. The basal metabolic rate was high. Bass stated that the condition constituted a clinical entity and should be classified as eosinophilic leukemia.

REPORT OF A CASE

N. P., aged 10 years, entered the Milwaukee Children's Hospital on Jan. 26, 1932. He complained of pain in the joints and legs. In October 1931 he had an attack of pain in the shoulders, hips and ankles. He was in bed four weeks. He returned to school but within two weeks he began to cough. The pains in the joints recurred and persisted. There was fever but no redness or swelling of the joints. The boy was kept in bed until January 22 (four days before admission to the hospital). The pains appeared in different joints, especially those of the spine. There was pain in the muscles of the thighs.

Physical Examination.—The boy was well developed and fairly well nourished. There was no tenderness or swelling of joints. There was a questionable cardiac murmur. He complained of pain in the left thigh. The spleen was somewhat enlarged.

Orthopedic Consultation.—An orthopedic examination showed slight atrophy of the left thigh as compared with right. There was slight weakness of the extensors of the left knee. There was more marked weakness of the flexors of this knee. There was also definite weakness in the adductors and flexors of the left hip as compared with the right. The impression was that these were manifestations of an old poliomyelitis.

Laboratory Data.—The reports from the laboratory were as follows:

January 27: There were 28,800 leukocytes, of which 75 per cent were eosinophils.

January 28: There were 23,200 leukocytes, of which 65 per cent were eosinophils, 12 per cent neutrophils, 1 per cent large mononuclear cells, 4 per cent large lymphocytes and 18 per cent small lymphocytes. The red cell count was 3,780,000, and the hemoglobin content was 65 per cent. X-ray films of the left knee and left hip disclosed no pathologic changes in the bones.

February 3: The Wassermann test was negative.

January 30: Examination of stools revealed encysted forms of Giardia Lamblia.

February 15: A piece of muscle was removed from the left thigh and sections were examined for Trichinella spiralis, but the organism was not found. A serum precipitin test for trichinosis as described by Augustine and Theiler [18] was negative. The basal metabolic rate (Boothby and Sandeford) on three different occasions was —2.9, —19.2 and —16.2 per cent.

February 26: The Mantoux test was negative. Cutaneous tests made with food extracts, pollens, house dust and other extracts revealed occasional mild reactions.

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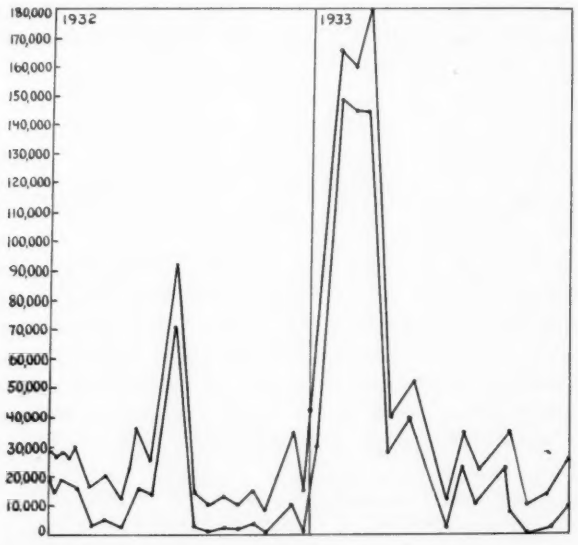
17. Hay, J., and Evans, W. H.: Quart. J. Med. **22**:167, 1929.

18. Augustine, D. L., and Theiler, H.: Precipitin and Skin Tests as Aids in Diagnosing Trichinosis, Parasitology **24**:60 (March) 1932.

Blood Counts: The accompanying table and chart may be consulted for the blood counts.

The boy's general health was good, and there was a steady gain in weight. He attended school regularly. When his white blood cell count was 180,400 with an



The upper curve represents the white blood cell count; the lower, the percentage of eosinophils.

Blood Counts

Date	White Blood Cells	Eosinophils, %	Date	White Blood Cells	Eosinophils, %	Date	White Blood Cells	Eosinophils, %
1/27/32	28,800	75	4/19/32	9,800	11	4/14/33	176,600	92
1/28/32	23,200	65	4/28/32	13,800	15	4/21/33	172,000	91
2/ 1/32	27,400	73	5/ 6/32	11,600	8	4/27/33	180,400	88
2/ 6/32	26,800	68	5/12/32	15,000	15	5/ 3/33	39,600	73
2/ 8/32	29,800	67	5/20/32	8,600	14	5/10/33	53,600	76
2/15/32	25,800	62	5/26/32	17,000	25	6/ 2/33	30,200	73
2/27/32	15,800	25	6/ 9/32	34,300	29	6/30/33	12,400	23
3/ 2/32	19,200	31	6/24/32	14,600	14	7/21/33	37,000	72
3/ 7/32	13,000	39	7/15/32	13,100	6	8/18/33	22,600	49
3/11/32	22,000	25	8/ 2/32	13,800	10	9/15/33	25,400	60
3/15/32	25,200	42	10/ 7/32	12,000	12	9/28/33	35,500	73
3/22/32	38,000	43	11/18/32	14,200	13	10/20/32	16,200	47
3/31/32	28,000	54	12/30/32	11,600	9	11/10/33	11,000	11
4/ 8/32	93,600	77	2/24/33	16,800	2	12/ 8/33	13,600	18
4/14/32	15,900	25	4/ 7/33	43,800	72	1/12/34	23,800	36

eosinophilia of 92 per cent his condition was good. He complained of backache at times, but no pathologic condition was demonstrated clinically or by x-rays.

Family.—The boy's father suffered from a disorder that had been diagnosed as tuberculosis. His older sister had a white cell count of 19,000 and an eosinophilia of 34 per cent. On all other occasions blood counts on the members of the family were normal.

COMMENT

The unusually high white cell count would lead one to regard this case as one of leukemia. Unlike the cases of Bass, however, the basal metabolic rate was never above normal. In fact, the rate was rather low on two occasions. The high metabolic rate in leukemia has been explained as a result of the rapid formation of young cells in the tissues. The eosinophils in the blood are of the mature type. In this case x-ray films of the chest did not reveal mottling as in the case reported by Bass. Gittins [19] stated that the duration of leukemia in children is short, being usually less than two months, and that basophils and eosinophils are more frequent in myelosis and may be more pronounced in chronic cases. In leukemia there are immature white blood cells, and these are more important in the diagnosis of the disease. In this case the eosinophils were of the adult type. The low metabolic rate, the absence of immature leukocytes in the blood and the long duration of the eosinophilia in this case are against the diagnosis of leukemia.

No satisfactory explanation may be given for this wild reaction on the part of the blood-forming organs as manifested by the high eosinophil count. That it was due to some form of allergy seems a possible explanation. The known allergic conditions cause eruptions of the skin, gastro-intestinal symptoms, pains in the muscles and joints or reactions in the organs of respiration. Heredity is an important factor in allergy. It is not unusual for several members of a family to have some manifestation of this condition. In familial eosinophilia, the reaction in the blood-forming organs resulting in hypereosinophilia may be the principal manifestation of an allergic reaction.

425 East Wisconsin Avenue.

19. Gittins, R.: Studies in Anaemias of Infancy and Early Childhood; Leukemia (Leucosis) in Children, Arch. Dis. Childhood **8**:291 (Oct.) 1933.

DIABETES MELLITUS NEONATORUM

REPORT OF A PROBABLE CASE

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The occurrence of diabetes mellitus in the neonatal period is extremely rare. In a review of the literature White [1] cited but three cases of congenital diabetes in which hyperglycemia was present at birth or shortly thereafter.

The following probable case of diabetes mellitus neonatorum was discovered in a colored female infant on the eleventh day of life.

REPORT OF CASE

History.—B. H., a colored female infant, was born on Dec. 29, 1932, at Gallinger Municipal Hospital. The father and mother were alive and said to be well. With the recent pregnancy the mother was observed in the prenatal clinic at Columbia Hospital for Women and Lying-in Asylum, and was found to be in good physical condition. There had been seven previous pregnancies, six of which resulted in the birth of children who were alive and said to be well, and one in a miscarriage of unknown cause.

The infant was born at term; labor was normal, and no postnatal complications were noted. The weight at birth was 7 pounds and 4 ounces (3,288.5 Gm.). The infant was breast fed.

Present Illness.—In spite of the fact that the child nursed well and the mother's milk was abundant, the infant failed to gain weight. She was admitted to the Children's Hospital on Jan. 9, 1933.

Physical Examination.—The patient was a poorly nourished, dehydrated colored female weighing 5 pounds (2,267.9 Gm.).

The temperature was 103 F. The respirations were rapid and irregular. The heart and lungs appeared normal. The liver and spleen were not enlarged. Both ear drums were acutely inflamed and bulging. Two small, irregularly oval areas of impetigo contagiosa bullosa were observed, one on the chin and one on the neck.

Laboratory Findings.—Examination of the blood showed 60 per cent hemoglobin, 3,750,000 erythrocytes and 10,800 leukocytes per cubic millimeter. There

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From the Medical Service of the Children's Hospital.

1. White, P.: Diabetes in Childhood and Adolescence, Philadelphia, Lea & Febiger, 1932, p. 41.

were 68 per cent lymphocytes and 32 per cent polymorphonuclear leukocytes, of which 18 per cent were lobulated, 12 per cent band forms and 2 per cent young forms.

Urinalysis revealed the presence of a large amount of albumin and granular casts as well as marked reduction of Benedict's solution.

A determination of the blood sugar on the day following admission showed 520 mg. per hundred cubic centimeters. The carbon dioxide-combining power was 28 volumes per cent.

Examination of the spinal fluid showed 55 cells, of which 64 per cent were polymorphonuclear leukocytes and 36 per cent lymphocytes. There was also marked increase in the globulin and sugar. No organisms were found on smear or culture.

The Wassermann reaction of the blood was negative.

X-ray pictures of the long bones revealed no pathologic changes.

Course and Treatment.—Bilateral myringotomy was performed on the day of admission, and pus obtained from each middle ear. Bilateral antrotomy was done two days after admission, and a considerable amount of pus and necrotic bone were found in each mastoid region.

An indwelling urethral catheter was inserted, and samples of urine taken at frequent intervals revealed varying degrees of reduction of Benedict's solution.

Small doses of insulin varying from 1 to 5 units were given subcutaneously. Under this therapy the blood sugar dropped to 35 mg. per hundred cubic centimeters of blood, but rose again to 280 mg. as soon as the dosage of insulin was reduced or the administration discontinued.

The patient's diet consisted of breast milk, which was taken fairly well, and water. Fluids in the form of physiologic solution of sodium chloride, 5 per cent dextrose and Hartmann's solution[2] were given subcutaneously and intraperitoneally. A transfusion of 40 cc. of citrated blood was given intravenously.

The condition of the patient became progressively worse. The respirations became very rapid and irregular, and there was almost complete suppression of urine. The impetiginous lesions spread rapidly to involve more than two thirds of the body's surface. The patient died on January 15.

Necropsy.—At necropsy the following conditions were noted: lobar and lobular pneumonia; fibrinous pleurisy; chronic passive congestion of the kidneys, spleen and liver; a patent foramen ovale; bullous impetigo, and evidences of a bilateral antrotomy.

Microscopic study of sections from the pancreas revealed an increased amount of interacinar fibrous tissue. The islands of Langerhans were greatly reduced in number.

Sections of renal tissue showed the glomeruli to be prominent as a result of round cell infiltration and engorgement of the tufts. There were also occasional capsular sclerosis and cloudy swelling of the tubular epithelium. The general appearance was that of subacute glomerular nephritis and chronic passive congestion.

Sections of the brain and suprarenal glands showed no pathologic changes.

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2. Hartmann's solution contains sodium chloride, sodium lactate, calcium chloride and potassium chloride.

SUMMARY AND COMMENT

1. The several infectious processes present in this case would not be likely to cause the large increase in blood sugar observed.

2. The pancreas showed changes which suggest a diabetic process.

3. The case was probably one of neonatal diabetes mellitus.

4. Urinalysis is recommended as a routine procedure in the examination of the newly born, with determination of the blood sugar if there is a suspicion of the presence of diabetes mellitus.

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ASSOCIATION OF UNIVERSAL EDEMA OF THE FETUS AND CONGENITAL ANEMIA OF THE NEW-BORN

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Within the past few years a triad of apparently closely associated disorders affecting the hematopoietic system of the fetus and the new-born infant has received considerable recognition in the pediatric literature. This group consists of universal edema of the fetus, familial icterus gravis neonatorum and congenital anemia of the new-born. Attention was early called to the relationship existing between universal edema of the fetus and icterus gravis neonatorum by the frequent familial incidence and the similarity of the pathologic pictures. However, congenital anemia of the new-born is a rather newly defined clinical entity, and its association with universal edema of the fetus and icterus gravis neonatorum has therefore only recently been appreciated.

Universal edema of the fetus [1] (congenital fetal hydrops) is a relatively rare condition that has been known for several centuries. The most striking feature of the disease is generalized edema. The liver and spleen are greatly enlarged. The placenta, too, is enlarged and edematous. Anemia, icterus and extensive extramedullary hematopoiesis are usually present. A familial incidence is frequent. The disease reaches its greatest severity in utero and generally results in the birth of a dead premature edematous fetus.

Icterus gravis neonatorum is characterized by severe jaundice that appears earlier, is more intense and persists longer than the ordinary physiologic icterus of the new-born. The vernix caseosa is usually yellow. A familial incidence, enlargement of the liver and spleen, anemia and extramedullary hematopoiesis occur as in fetal hydrops. Although the mortality is high, the disease is less serious than universal edema of the fetus.

From the Departments of Obstetrics and Pediatrics of the Morrisania City Hospital.

1. Clifford, S. H., and Hertig, A. T.: Erythroblastosis of the Newborn, New England J. Med. **207**:105 (July 21) 1932. Clifford and Hertig found an incidence of one in twelve hundred births. They quoted the experience of others as varying from one in two thousand to one in three thousand births.

Congenital anemia of the new-born is the mildest disorder of the group. Its only constant and characteristic symptom is a severe anemia occurring shortly after birth in an infant in whom the accepted causes of secondary anemia can be excluded, chiefly sepsis, syphilis and hemorrhagic disorders. Erythroblasts may be present in the circulating blood. Mild icterus, enlargement of the liver and spleen and extramedullary hematopoiesis are of frequent occurrence. A familial incidence has been noted by several authors.[2] The first case of congenital anemia of the new-born to be described in detail was reported by Ecklin [3] in 1919, although at an earlier period authors had suggested that such a condition might occur. Donnally [4] reported another case in 1924. From then on additional cases were gradually added by other authors. In 1931 we [5] succeeded in collecting from the literature twenty-eight authentic instances of which only half had been reported in detail. Since that time the number of reported cases has more than doubled.

The term "erythroblastosis fetalis" expresses the pathologic rather than the clinical aspect of these disturbances of erythropoiesis. The salient features are enlargement of the liver and spleen, pallor of the body tissues, numerous erythroblasts in the blood and extramedullary hematopoietic activity in the liver, spleen, kidneys and other organs. Jaundice and generalized edema are usually present, although the edema may occasionally be absent. Enlargement and edema of the placenta complete the picture.

In their recent excellent analytic review, Diamond, Blackfan and Baty [2a] attempted to prove, on the basis of a common underlying pathologic condition (erythroblastosis), the close association of universal edema of the fetus, icterus gravis neonatorum and anemia of the new-born by showing first the relationship of universal edema of the fetus to icterus gravis neonatorum and then the relationship of icterus gravis neonatorum to congenital anemia of the new-born. From this study they deduced that universal edema of the fetus must be related to anemia of the new-born.

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2. (*a*) Diamond, L. K.; Blackfan, K. D., and Baty, J. M.: Erythroblastosis Fetalis and Its Association with Universal Edema of the Fetus, Icterus Gravis Neonatorum and Anemia of the New-Born, J. Pediat. **1**:267 (Sept.) 1932. (*b*) Segar, L. H., and Stoeffler, W.: Anemia of the Newborn in Three Successive Siblings, J. Pediat. **1**:485 (Oct.) 1932. (*c*) Bonar, B. E., and Smith, E. H.: Anemia in the Newborn, Am. J. Dis. Child. **45**:594 (March) 1933. (*d*) Happ, W. M., in Round Table Conference on Disorders of the Blood and the Hemopoietic System, J. Pediat. **1**:638 (Nov.) 1932.

3. Ecklin, T.: Ein Fall von Anämie bei einem Neugeborenen, Monatschr. f. Kinderh. **15**:425, 1919.

4. Donnally, H. H.: Anemia in the New-Born, Am. J. Dis. Child. **27**:369 (April) 1924.

5. Pasachoff, H. D., and Wilson, L.: Congenital Anemia of the New-Born, Am. J. Dis. Child. **42**:111 (July) 1931.

We wish to report a case that offers further evidence of the existence of this relationship. So far as we are able to determine after a review of the literature, this is the first instance on record of the occurrence of universal edema of the fetus and of congenital anemia of the new-born in offspring of the same parents, that is, universal edema in one sibling and anemia of the new-born in another. Another noteworthy aspect of our cases is that erythroblastosis was not present in either child. In 1931 we reported a case of profound anemia in a new-born infant, the second child of healthy parents. The first baby is alive and well. The second child died on the fifth day, and at autopsy none of the usual causes of secondary anemia could be discovered. The spleen, the bone marrow and, to less extent, the liver showed a myeloid reaction with practically no response on the part of the erythrocytogenic system. We are now in a position to report two subsequent pregnancies in the same mother, both pregnancies terminating in the birth of dead premature infants with generalized edema.

REPORT OF A CASE

M. P., a white woman, aged 31, was admitted to Morrisania City Hospital during her fourth pregnancy, on April 22, 1933. With the exception of the obstetric history, the patient's history and the family history were unimportant. The first pregnancy in 1929 resulted in a normal, full-term, living infant. The second child was born at full term on May 26, 1930. This infant, who died on the fifth day, had congenital anemia. Detailed laboratory data were given in a previous report.

The third pregnancy terminated spontaneously on Aug. 6, 1931, with the delivery of a 6 month fetus at stillbirth. The fetus was edematous and macerated. The placenta showed no gross abnormalities. Microscopic examination was not made.[6]

The patient again became pregnant and was under observation at the Bronx Maternity Hospital from Jan. 9 to April 21, 1933. The prenatal course was normal until April 20, when fetal movements stopped. Two days later, or six weeks prior to term, labor began spontaneously. The patient was admitted to the Morrisania City Hospital and one hour later was delivered of a macerated, edematous fetus. The amniotic fluid was blood stained.

Physical examination of the mother at this time gave negative results. The blood pressure was 120 systolic and 90 diastolic. The urine was normal. The blood chemistry showed urea nitrogen, 13 mg.; creatinine, 1 mg., and sugar, 95 mg. per hundred cubic centimeters. The blood count showed: red blood cells, 4,000,000; hemoglobin, 80 per cent; white blood cells, 9,600; polymorphonuclear neutrophils, 80 per cent; monocytes, 5 per cent; lymphocytes, 14 per cent, and basophils, 1 per cent. The reticulocytes numbered 2 per cent and the platelets, 290,000. No abnormal cells were noted in the blood smear. The Wassermann tests of the blood and spinal fluid were negative. The cell count of the spinal fluid was 3 per cubic millimeter; globulin and sugar were normal.

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6. This report was supplied by the Norwegian Lutheran Deaconesses' Hospital, Brooklyn.

The placenta was soft and grayish and twice the normal size. Several hours following the expulsion of the placenta, a large succenturiate lobe was passed. The placenta contained no infarcts. It was 30 cm. in diameter and 5.5 cm. in thickness. On microscopic examination the placenta showed numerous areas of edema of the chorionic villi. Erythroblasts were not observed in the placental capillaries.

The puerperium of the patient was uneventful.

Autopsy [7] was performed on the fetus several hours after delivery, and a report was made as follows: The body was that of a slightly premature white female infant weighing 6½ pounds (2,948 Gm.), with a total length of 40 cm. The skin was macerated and of a deep pink hue. There was marked edema of the face, abdomen and extremities.

The pericardial, pleural and peritoneal cavities were filled with a reddish-brown fluid which gave a strongly positive reaction to the benzidine test, but a negative

Fig. 1.—Section of the placenta, showing edema of the chorionic villi; low power magnification.

reaction to the test for bile. Microscopic examination of the fluid showed only débris; no cells were found in the stained smear of the sediment.

The lungs were pink and unexpanded. The heart was normal. The liver was soft, grayish and slightly enlarged. The spleen was soft and pale gray and enlarged to one and one-half times the normal size. The kidneys were of normal size and lobulated. The pancreas, gastro-intestinal tract, uterus and adnexa appeared to be normal. The brain showed no gross abnormalities. The bone marrow grossly also appeared normal.

Microscopically,[8] all of the organs were in a state of moderately advanced autolytic degeneration. The spleen especially was so degenerated that cellular

7. Dr. William Aronson, pathologist to the Morrisania City Hospital, supplied the pathologic report.

8. The sections were stained by the Giemsa method.

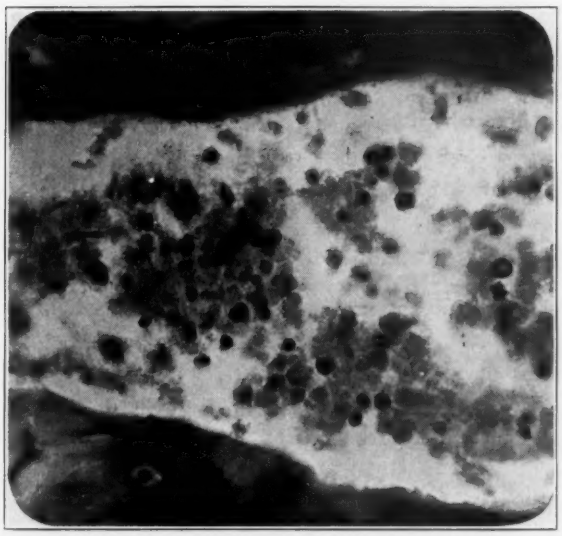

Fig. 2.—Section of the bone marrow, showing no increase in the number of erythroblasts.

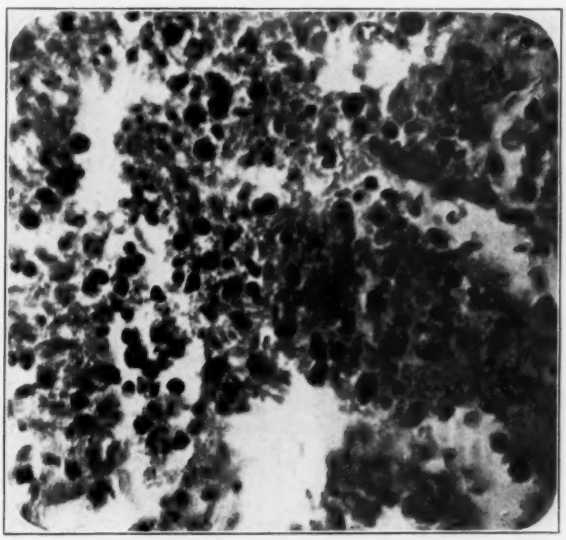

Fig. 3.—Section of the liver, showing no increase in the number of erythroblasts.

identification was impossible. Although the sections of the bone marrow and liver contained many nucleated erythrocytes and immature leukocytes, the cells were considerably fewer in number than are seen in the normal fetus at a corresponding stage of development. However, because of the degeneration of the tissues, it was impossible to state definitely that there was a decrease of the hematopoietic elements. No areas of blood formation were observed in the kidneys. Microscopic examination of the blood from the heart showed only débris; no cellular elements could be identified.

COMMENT

The familial association has been advanced as one of the prominent common factors in support of the contention that universal edema of the fetus, icterus gravis neonatorum and congenital anemia of the new-born are different clinical varieties of the same pathologic process. Although cases of universal edema and icterus gravis, as well as cases of icterus and anemia of the new-born, have occurred in different offspring of the same parents, the combination of universal edema and anemia of the new-born appears to be extraordinary. The trend has been to repeated mild or repeated severe forms of the disease in the same family. The occurrence of the mild grades (anemia without edema or severe icterus) and the severe grades (hydrops) of the disease in siblings is unique.

Another feature that has been advanced as an important link in the chain of evidence connecting the triad under discussion is erythroblastosis. This presumably is due to an unknown stimulus that causes a persistence of, or a reversion to, the embryonic level of blood formation.[9] Although erythroblastosis has been suggested as the underlying pathologic condition of the group, there are definite objections to this concept. A number of cases of each of the three disorders in which there has been no abnormal erythroblastic activity have been reported. Our cases of congenital anemia and that of fetal hydrops failed to show evidence of erythroblastosis. In addition, it is to be recalled that erythroblastosis is by no means pathognomonic of this group of disorders, for it occurs in other conditions as well, notably congenital syphilis and sepsis of the new-born. It thus appears that erythroblastosis is probably only a concomitant feature and represents a response on the part of the erythropoietic system to an increased call for red blood cells.

That erythroblastosis is a secondary response to hemolysis is the view expressed by Parsons, Hawksley and Gittins[10] in a recent study

9. Abt, A. A.: Erythroblastosis in Icterus Gravis Neonatorum, J. Pediat. **3**:7 (July) 1933. Diamond, Blackfan and Baty.[2a]

10. Parsons, L. G.; Hawksley, J. C., and Gittins, R.: The Hemolytic (Erythronoclastic) Anemias of the Neonatal Period, with Special Reference to Erythroblastosis of the Newborn, Arch. Dis. Childhood **8**:159, 1933.

of the anemias of childhood. They classified anemia of the new-born as hemolytic anemia because, they contended, it is difficult to conceive of anemia developing rather suddenly and after a few days in an infant who appeared normal at birth, unless there has been hemorrhage or hemolysis. Severe hemolysis need not be followed by marked jaundice, according to these authors, if it occurs gradually and the liver is able to excrete the bilirubin.

According to Stransky,[11] the association of erythroblastosis with congenital anemia of the new-born is not constant. Stransky has divided the congenital anemias of the new-born into two groups. The first and more common type is characterized by an aregenerative blood picture with complete absence of embryonal forms. Stransky stated the belief that this type is due to an insufficiency of the function of the bone marrow. Although spontaneous cures occur, it is often necessary to resort to blood transfusions to initiate recovery. The second and more serious type is associated with an embryonic blood picture and is related to erythroblastosis. In our case of congenital anemia, which definitely falls into the aregenerative group, there was nevertheless a fatal outcome.

SUMMARY

As a sequel to a case of congenital anemia of the new-born reported by us in 1931, we have reported two subsequent pregnancies in the same mother, both of which resulted in premature stillborn infants with universal edema. This familial incidence supports the contention made by several authors that universal edema of the fetus and congenital anemia of the new-born are closely related disorders. There was no evidence of abnormal erythroblastic activity in our cases.

11. Stransky, E.: Beiträge zur klinischen Hämatologie im Saüglingsalter: Ueber die primäre Anämie der Neugeborenen, Ztschr. f. Kinderh. **51**:239, 1931.

CEREBRAL SEQUELAE OF ICTERUS GRAVIS NEONATORUM AND THEIR RELATION TO KERNIKTERUS

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In a previous communication [1] we expressed the opinion that jaundice of the nuclei of the brain, a condition frequently referred to as kernikterus, is the result of an injury to those cellular masses during which they become stained secondarily with bile pigments. Pigmentation in this condition probably occurs in the same way that intravital dyes generally localize in zones of injury. It was pointed out that kernikterus occurs almost exclusively in association with icterus gravis neonatorum and that infection may be the etiologic factor in many cases of the latter condition.

Conceptions of the pathogenesis of the underlying cerebral injury are, at best, hypothetic. Among the possible pathogenic factors may be mentioned: (1) postinfectious encephalitic processes; (2) cerebral birth trauma or asphyxia and (3) cerebral cellular maldevelopment. Whether the bile pigments, aside from their staining properties, play a significant rôle in the subsequent evolution of the clinical or anatomic picture is not clear. Against the concept that their part is purely passive is the fact that a similar pathologic picture as regards localization of the lesions and cellular changes, but without icteric pigmentation, has not been demonstrated in the neonatal period.

The clinical and anatomic observations on children with kernikterus who die during the first or second week of life have been described elsewhere.[1] Our interest at present lies in those children who survive a severe neonatal illness characterized by intense jaundice (clinically designated as icterus gravis neonatorum), but who subsequently present clinical evidence of extensive cerebral damage. The possible relationship between this condition and kernikterus will be discussed later.

From the Departments of Pathology and Pediatrics, Yale University School of Medicine, and the pathological and pediatric services of the New Haven Hospital and Dispensary.

1. Zimmerman, H. M., and Yannet, Herman: Kernikterus: Jaundice of the Nuclear Masses of the Brain, Am. J. Dis. Child. **45**:740 (April) 1933.

Cases of this kind have been described by Guthrie,[2] Spiller,[3] Paul,[4] De Lange,[5] Hoffmann and Hausmann[6] and Greenwald and Messer.[7] However, there have been no anatomic studies reported of the cerebral lesions present in cases of this kind. Such a study, the presentation of which is the basis of this communication, was made on the patient in case 4 of our previous report, when the child came to necropsy at 3 years of age.

REPORT OF A CASE

History and Course.—The parents were healthy. Wassermann and Kahn tests on the mother's serum gave negative results. One previous child, born prematurely (8 months) in March 1927, died at the age of 18 days. The clinical diagnosis was icterus gravis; no other details were available. The subject of this report was the product of the second pregnancy (March 1930). The mother became pregnant a third time in 1932, and was delivered of a premature female child (6½ months). The child died twenty-four hours after birth, and showed extensive pulmonary atelectasis on postmortem examination.

The second pregnancy terminated five weeks prematurely with the spontaneous delivery of the patient. Labor was uncomplicated and lasted about one-half hour. The child weighed 5½ pounds (2,493 Gm.) and showed no abnormalities. Except for mild jaundice, the first week of life was uneventful. At the end of this time, there developed severe icterus which persisted for the next three weeks. There was a constant but irregular elevation of the temperature, which at times reached 106 F. Vomiting, described as projectile on occasions, was frequent. The respirations were irregular, with occasional periods of apnea. At no time were there convulsions. The symptoms gradually subsided, and by 1 month of age recovery was practically complete, according to the aunt, a registered nurse.

The subsequent course was apparently normal until the child was 5 months of age. At this time, she began to have "spells" lasting about ten seconds, during which she became moderately rigid without convulsions. The spells occurred frequently and were precipitated usually by some stimulus like handling of the infant or a sudden loud noise. At about the same time she began to have athetoid movements of the arms. The spastic spells and athetosis persisted. There was no effort to speak or to sit up. It was felt that the child's vision was impaired. The patient was admitted to the hospital in November 1931, when 20 months of age.

Physical Examination.—On admission examination revealed a markedly malnourished and obviously mentally retarded child. Except for signs pointing to

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2. Guthrie, L.: Case of (?) Kernikterus Associated with Choreiform Movements, Proc. Roy. Soc. Med. **7**:86, 1913.

3. Spiller, W. G.: Severe Jaundice in the Newborn Child a Cause of Spastic Cerebral Diplegia, Am. J. M. Sc. **149**:345, 1915.

4. Paul, S.: Zur Symptomatologie der Wilsonschen Krankheit im Kindesalter, Arch. f. Kinderh. **74**:38, 1924.

5. De Lange, C.: Extrapyramidale Bewegungsstörungen bei Sepsis neonatorum, Acta pædiat. **4**:60, 1925.

6. Hoffmann, W., and Hausmann, M.: Ikterus neonatorum gravis: Folgezustände und Pathogenese, Monatschr. f. Kinderh. **33**:193, 1926.

7. Greenwald, H. M., and Messer, W.: Icterus Neonatorum Gravis: Report of a Case Which Recovered with Sequelae Pointing to an Involvement of the Central Nervous System, Am. J. M. Sc. **174**:793, 1927.

diffuse involvement of the central nervous system, no abnormalities were found. There were constant athetoid movements of the arms which varied in severity at different times. Manipulation would result in generalized spasticity with moderate opisthotonos which lasted for about fifteen seconds and then gradually receded, but did not disappear completely. The spells occurred apparently spontaneously at infrequent intervals. The deep reflexes were active and equal on the two sides. The abdominal reflexes were present and moderately active. There was no ankle clonus, and the Babinski responses were flexor in type. The eyegrounds revealed a moderate pallor of the disks, both of which were well outlined. Vision was markedly impaired. There was a constant, roving nystagmoid movement of both eyes. The pupillary reflexes were normal.

Course.—The child's stay in the hospital was marked by a moderately severe febrile illness of unexplained etiology which had no apparent effect on, or relation to, the nervous condition just described. She was discharged ten days after admission without significant change. The laboratory examination, which included complete examinations of the blood, urine and spinal fluid, gave negative results.

The child was seen again on March 21, 1932, when she was 2 years of age. There had been no significant change in the clinical picture. Athetosis and spasticity were present with the same degree of severity. The child had made no effort to speak, and there was apparently no change in the mental status.

From March 1932, the patient's course was slowly but progressively down-hill. Although no evident infection was present, the child frequently had an elevated temperature, which often reached 106 F. From November 1932 until the child's death in March 1933, the temperature was almost always between 102 and 106 F. There was no gross change in the neurologic status. The rigidity of the extremities and back remained about the same. There were no convulsions. Mentally, there was no progress, the child showing almost no evidence of perception of her surroundings. Occasionally she regurgitated dark brown material. From January 1933 until death, edema of the extremities and face was noted. The intake of food during this period was greatly reduced, owing to dysphagia and frequent regurgitation. The child died suddenly on March 8, 1933, when 3 years of age. There had been no change in the condition, except for the edema, during the preceding four weeks.

Necropsy.—The examination was performed ten hours post mortem by Dr. Béla Halpert.

The body was that of a poorly developed, much emaciated white girl, weighing 17 Kg. (37 lb.) and measuring 84 cm. (33.5 inches). The skin was extremely pale but not icteric. Most of the deciduous teeth were present, but their crowns were almost entirely worn down. The chest was rather flat and on a level with the abdomen. An ulcer 1 cm. in diameter was present on the right labium majus, which appeared to be slightly swollen. Another ulcer, 16 by 8 mm., was found in the gluteal fold; the surface was covered with a purulent exudate. Marked pitting edema was present over the dorsa of the feet and over the ankles and extended half-way to the knees. There was marked scoliosis of the thoracic portion of the vertebral column, with the convexity to the right. There were a sacral decubitus 4 by 2 cm. and smaller decubiti over each greater trochanter. The peritoneal cavity contained 50 cc. of light yellow, clear fluid; the abdominal viscera were normally disposed. There was practically no thymic tissue. Each pleural cavity contained about 40 cc. of clear fluid, and the pericardial sac contained 20 cc. of similar fluid.

Both lungs were the seat of early focal pneumonia. The entire gastro-intestinal tract was lined by intact mucosa. The liver was normal in the gross and on microscopic examination. The right suprarenal gland contained a hemorrhagic infarct, and it was found that its vein was completely thrombosed. The thrombus extended into and almost completely occluded the inferior vena cava from the junction of the renal veins to a point 4 cm. above the junction of the common iliac veins. The thrombus was gray and showed some evidence of organization microscopically. Several of the smaller veins in the left renal pelvis were thrombosed, but there was no hemorrhage or necrosis in the left kidney. The esophagus was markedly distended, measuring 6 cm. in diameter; its wall was greatly thickened as a result of an increase of connective tissue and hypertrophy of the muscular coats.

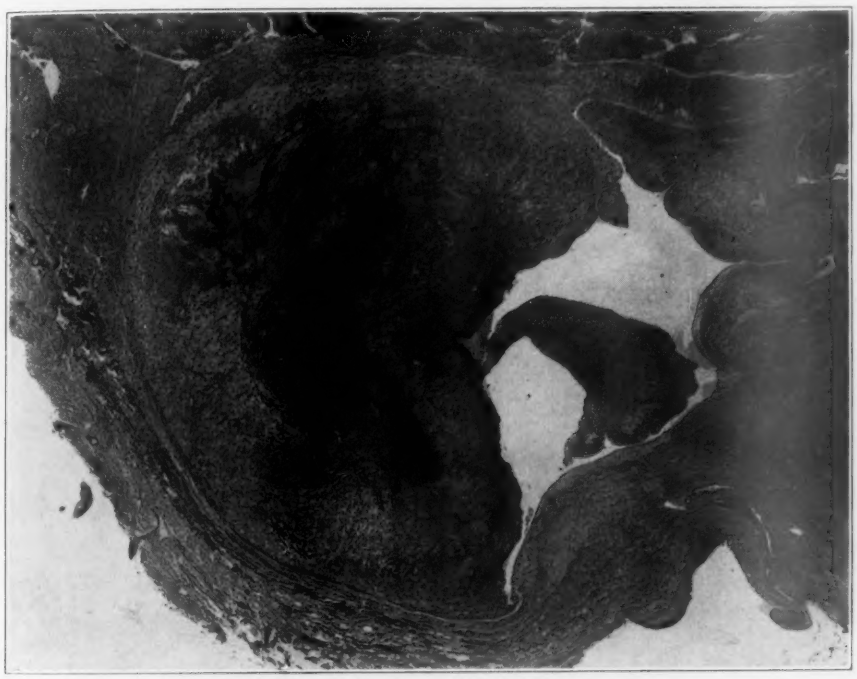

Fig. 1.—An organizing thrombus in the superior longitudinal venous sinus, filling about two thirds of the lumen. Hematoxylin and eosin stain; × 18.

The brain was well developed and symmetrical. The cerebral convolutions were of normal size and were not malformed. There was no evidence of old or recent hemorrhage in the cerebral meninges, which were delicate and translucent. The smaller pial blood vessels and the arteries at the base of the brain were not anomalous or occluded, but a gray thrombus filled approximately two thirds of the lumen of the superior longitudinal venous sinus (fig. 1). The thrombus was attached on three sides to the wall of the vessel and was being organized by proliferating fibroblasts and capillaries. A sheath of fibroblasts grew along the free surface of the clot, completely encapsulating it. There was no leukocytic reaction in either the wall of the vessel or the thrombus; indeed, all earmarks of an inflammatory reaction were absent.

The optic nerves and chiasm appeared to be atrophic and rather soft in the gross. Spielmeyer preparations revealed widespread patches of demyelinization (fig. 2) which contained increased numbers of interstitial cells. Many of the medullary sheaths were fragmented and formed round balloons. The nerves presented a spongy appearance because of large numbers of cystic cavities, most of which were empty, but some of which contained fragments of myelin and a few mononuclear phagocytes. In sudan III preparations, small collections of unphagocytosed fatty globules were found in the foci of degeneration, but some of the fat lay within mononuclear cells around blood vessels and between the rows of medullated nerve fibers.

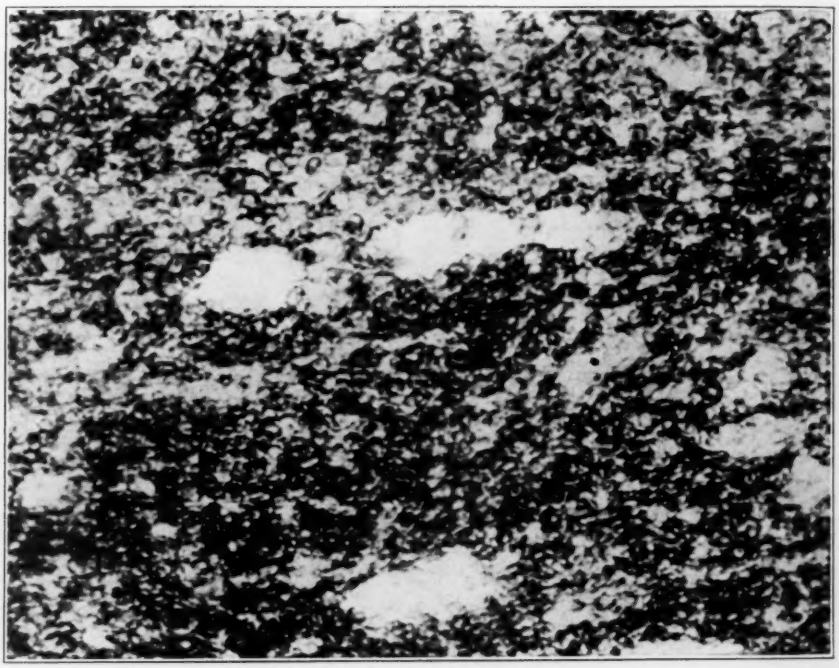

Fig. 2.—Demyelinization of the optic nerve. Spielmeyer stain; × 250.

On section, the cerebral cortex did not appear to be abnormal, nor were any changes noted macroscopically in the basal ganglions. The substantia nigra appeared to be absent. The posterior horns of both lateral ventricles were strikingly dilated as the result of shrinkage of the surrounding white matter, which was soft and necrotic. Kulschitzky preparations of these zones showed much evidence of destruction of the medullary sheaths (fig. 3). The process appeared to be old, since but few phagocytes were present in the zones of softening.

Changes of significance were not seen macroscopically in the brain stem and cerebellum. The spinal meninges were not abnormal. On section, poor demarcation was noted between the gray and the white matter of the thoracic portion of the spinal cord. Microscopically, the cervical, thoracic and lumbar portions of the spinal cord stained by the Kulschitzky and Spielmeyer methods revealed far advanced degeneration of the fiber tracts on the lateral sides (fig. 4). Those most

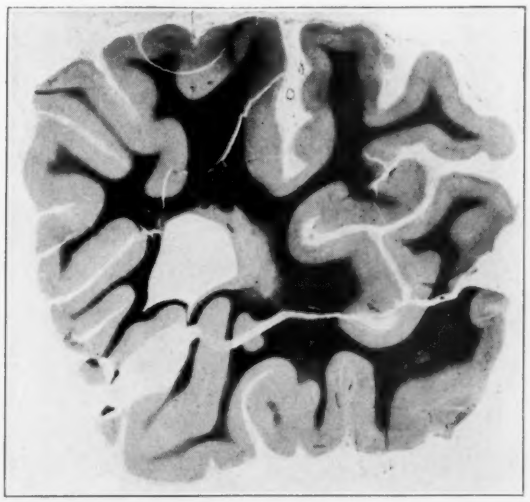

Fig. 3.—Destruction of the white matter around the posterior horn of the lateral ventricle. Kulschitzky stain; × 1.

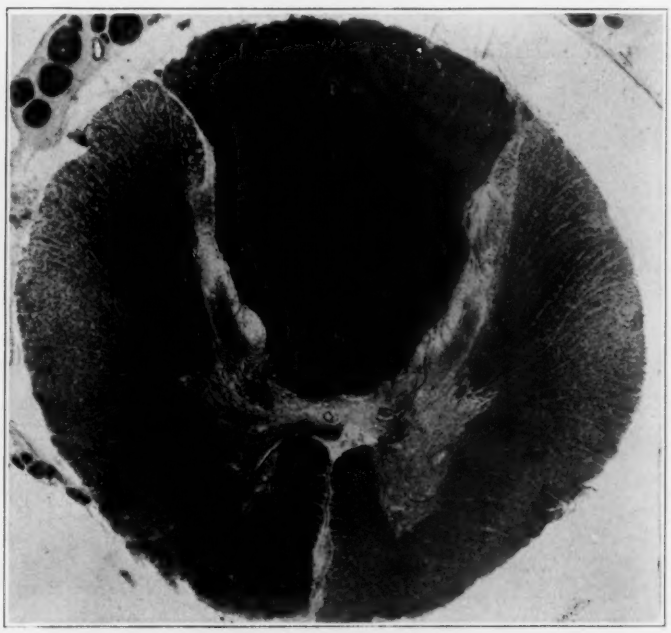

Fig. 4.—A transverse section of the thoracic portion of the spinal cord, showing degeneration of the rubrospinal, reticulospinal and spinocerebellar tracts. Kulschitzky stain; × 4.

Fig. 5.—Disappearance of the ganglion cells in the fascia dentata and in the end-plate of the lamina parietalis of the cornu ammonis. Nissl stain; × 40.

Fig. 6.—The globus pallidus, showing an almost complete absence of ganglion cells. Nissl stain; × 45.

involved were the rubrospinal tracts, but the reticulospinal and the spinocerebellar tracts were also partially demyelinated. A mild degree of degeneration was demonstrable in the zona terminalis, where numerous fragments and balloons of myelin were seen. Sudan III preparations revealed little fat in the spinal cord.

The cerebral parenchyma, although revealing no macroscopic evidence of alteration, was subjected to a detailed histologic study. The basal ganglions on the right were cut serially and stained by the Kulschitzky method; those on the left were sectioned similarly and stained by the Nissl method. The superior part of the mesencephalon was also prepared for serial study. Most of the cerebral cortex presented a normal cyto-architecture, but the cortical laminae were more narrow than usual. There was no evidence of necrobiosis of cortical ganglion cells, and

Fig. 7.—Absence of myelinated fibers in the globus pallidus or "status dysmyelinisatus" of Vogt. Kulschitzky stain; × 1.

there was no increase in the number of glia. The subcortical white matter showed no degenerative changes. The blood vessels of the brain and spinal cord and of their coverings were normal.

In the cornua ammonis, the fascia dentata and the end-plate of the lamina parietalis were completely destroyed (fig. 5). This occurred as the result of necrobiosis; there was no softening in this region and no proliferative reaction on the part of the glia. The lesion consisted simply of a loss of the nerve cell elements.

Of the nuclear masses constituting the basal ganglions, the claustrum and amygdaloid nuclei alone presented a normal microscopic appearance. The corpus striatum was lacking in large nerve cells, although there appeared to be no decrease in the number of small ganglion cells in either the caudate nucleus or the putamen.

Fig. 8.—The corpus subthalamicum (Luysi). A few surviving ganglion cells fringe the lower border. Nissl stain; × 40.

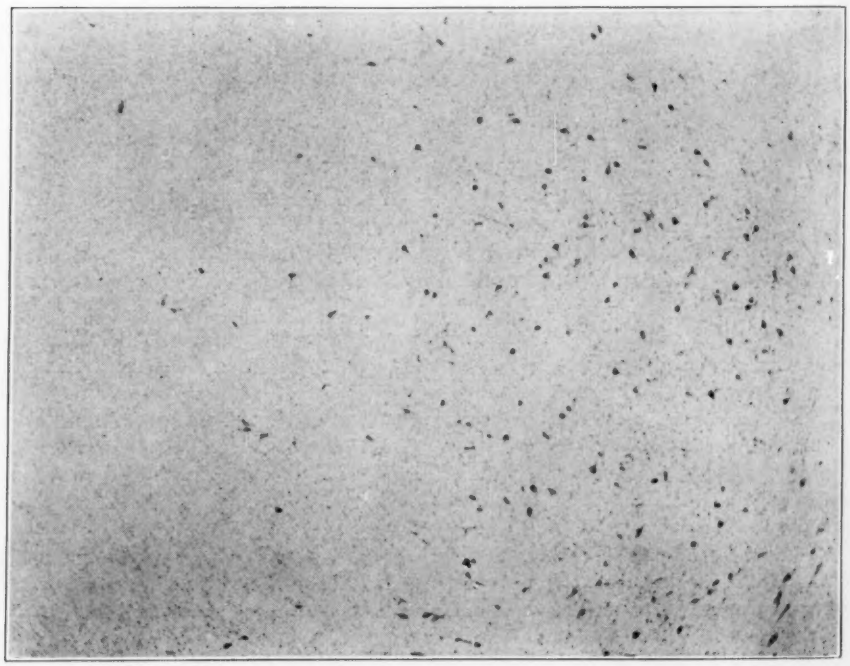

Fig. 9.—Marked paucity of ganglion cells in the nucleus ruber. Nissl stain; × 40.

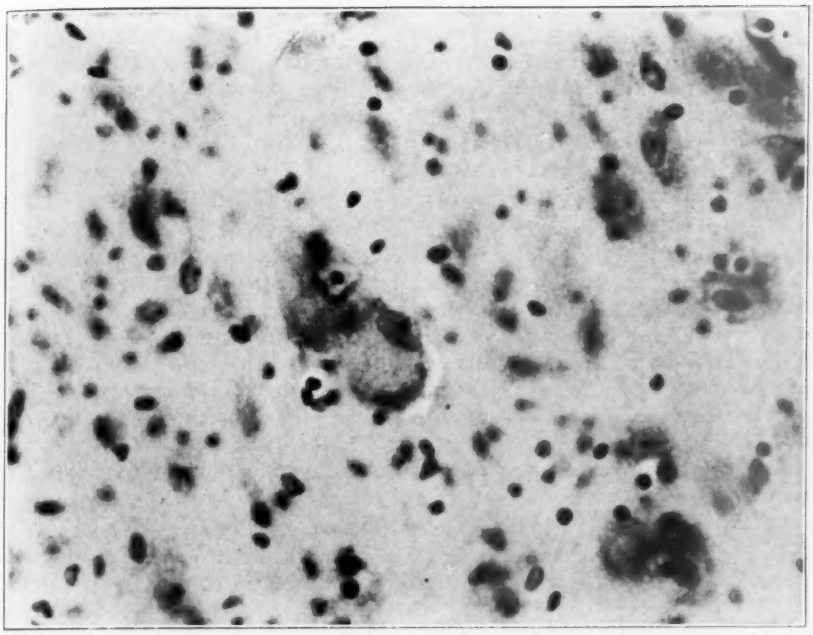

Fig. 10.—Swollen ganglion cells with eccentric nuclei in the mamillo-infundibular nucleus. Nissl stain; × 450.

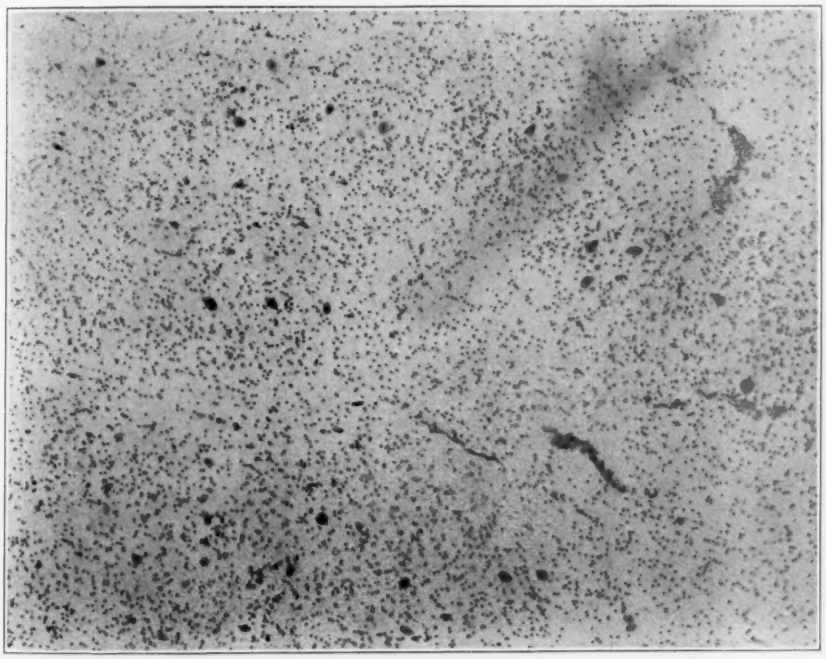

Fig. 11.—The dentate nucleus of the cerebellum. Note the decrease in the number of ganglion cells. Nissl stain; × 75.

The globus pallidus was completely devoid of both large and small ganglion cells (fig. 6). Kulschitzky preparations of the corpus striatum revealed a nearly normal complement of myelinated fibers in the caudate nucleus and putamen, but such fibers were absent in the globus pallidus (fig. 7). The adjacent internal capsule, however, was normally myelinated. It was striking that with all the degeneration of the medullated nerve fibers there was no vestige of phagocytosis.

The lateral thalamic nucleus was also the seat of necrobiotic changes in the ganglion cells. Large, acellular patches lay scattered irregularly in the nucleus. The mesencephalon revealed three striking changes: one was the almost complete disappearance of the corpus subthalamicum (fig. 8); another was the marked paucity of ganglion cells in the red nucleus (fig. 9), and the third was the absence of the substantia nigra. In the substantia nigra a few nerve cells were still intact in the medial half of the body. The stratum griseum centrale was unaltered. The cells of the mamillo-infundibular nucleus of the hypothalamic group were few, and those present were rounded and swollen (fig. 10). The cytoplasm of these cells was homogeneous and had a ground glass appearance. The nuclei were pale and were in eccentric positions within the cell bodies.

The nuclei of the third cranial nerve were intact, as were the pontile nuclei, the nuclei of the cranial nerves in the medulla and those of the anterior and posterior horns of the spinal cord. An entirely normal picture was found in the inferior and accessory olives of the medulla. There were no changes in the cerebellar cortex, but the dentate nuclei (fig. 11) contained few ganglion cells and no increase in the number of glia. The few ganglion cells remaining were abnormally pale and poorly stained.

The loss of ganglion cells in each nucleus described previously was due to necrobiosis. Nowhere was there parenchymal softening, nor were there proliferative changes on the part of the glia. Owing to the loss of the nerve cells, there was frequently a condensation of the normal glia of the zone involved, but there were no pathologic glia found. This was true also of the large cells of the Alzheimer variety.

COMMENT

In our previous report,[1] after a review of the literature, a summary of a group of cases of cerebral disease following severe neonatal jaundice was presented. The important clinical data collected in that paper may be briefly recapitulated as follows: Relatively soon after apparent recovery from an illness diagnosed as icterus gravis neonatorum, evidence of cerebral malfunction may develop. The manifestations include mental retardation, muscular spasticity, which is usually of the extrapyramidal type, athetosis, convulsions and, later, emotional instability. Because some of the cases of icterus gravis ending fatally within the first two weeks of life show, among other things, jaundice of the basal ganglions (kernikterus) and because some of the symptoms presented by the aforementioned group suggest damage of the basal ganglions, they were tentatively collected under the heading "recovered cases of kernikterus." From a clinical standpoint, the case which forms the basis of this communication falls into this category.

Is it possible to correlate the anatomic changes in this case with those found in kernikterus? The pathologic changes in kernikterus which must be considered are: the pigmentation, the peculiar localization of the lesions, the microscopic alterations in the ganglion cells and the glial response. Owing to the relatively long time which elapsed between the staining with bile pigments and the death of the child, the absence of cerebral pigmentation was to be expected. There is a striking similarity in the localization of the lesions in this instance and the usual localization of jaundice in kernikterus. The most frequently encountered zones of involvement in the latter condition, as has been pointed out previously, are the caudate nuclei, putamina, pallida, hypothalamic nuclei, cornu ammonis and dentate nuclei of the cerebellum. In the case presented, these areas are the ones primarily involved. Another zone of predilection in kernikterus is the periventricular white matter, which in this case shows extensive change. So striking a similarity can hardly be accidental. The histopathologic changes in kernikterus are essentially: (1) swelling of the ganglion cells progressing to complete cytolysis, the altered cells being stained yellow; (2) pigmentation of the interstitial tissues, and (3) the presence of large mononuclear glial phagocytes. Such changes could be expected to result in widespread loss of ganglion cells and their medullated fibers without any progressive reactions on the part of the glia. These are precisely the changes noted in the case described here. Although the evidence is mainly presumptive and must necessarily remain so until more material of a similar nature can be studied, it is highly suggestive of an intimate relationship between this case and kernikterus.

In this connection, the case reported by Burghard and Schleussing [8] of icterus gravis neonatorum with cerebral involvement, which ended fatally at the age of 5 months, is of great interest. The patient was a full term infant who became jaundiced during the first day of life. Icterus was marked by the fourth day; the respirations were irregular, and swallowing was difficult. Muscular spasticity developed and persisted until death. At necropsy the pallidum, corpus Luysi and cornu ammonis showed gray discoloration. The optic thalami, periventricular gray matter and dentate nucleus were similarly, although less extensively, involved. The white matter was intact except for small foci of gray-yellow softening. The basal nuclei were not jaundiced, but the ganglion cells were shrunken and showed loss of tigroid substance. The involved portions of the brain contained numerous fat granule cells. The changes in this case are of importance because of their resemblance to the picture encountered both in patients with kernikterus and in our own patient. It seemingly represents an intermediate phase of the pathologic process.

8. Burghard, E., and Schleussing, H.: Folgezustände des Icterus neonatorum gravis, Klin. Wchnschr. **12**:1526, 1933.

The fairly constant hyperthermia which was present during a large part of the clinical course in this case was never satisfactorily explained on the basis of a localized inflammatory process or septicemia. The degenerative changes in the mamillo-infundibular nucleus of the hypothalamic group are of decided interest in this connection. Recent experimental and clinical evidence seems to point to this nucleus as a controlling factor in thermoregulation. The thrombosis of the inferior vena cava and longitudinal venous sinus found at postmortem examination was evidently of recent origin, was not accompanied by inflammatory changes in the walls of the vessels, and was perhaps related to the marasmic condition of the child in the terminal period of life.

Since Wilson's disease and the related condition of pseudosclerosis have occasionally been mentioned in connection with kernikterus, it must be mentioned, in passing, that our patient failed to show either Alzheimer's glia or hepatic cirrhosis, which are the sine qua non of these conditions.

Spasticity and athetosis secondary to demyelinization of the pallidum, present in our patient, were first described as a clinico-anatomic entity by C. and O. Vogt,[9] under the designation of status dysmyelinisatus of the pallidum. A history of icterus gravis was not mentioned in their two patients, and the pathogenesis of the lesion was obscure in their cases and in the few cases of a similar nature reported subsequently by other writers. Our case is of some importance, therefore, for the evidence it brings to bear on the rôle which kernikterus may play in the pathogenesis of this pallidal lesion.

SUMMARY

The history is presented of a child in whom following apparent recovery from a severe neonatal illness clinically diagnosed as icterus gravis neonatorum there developed signs of extensive cerebral dysfunction. The neurologic phenomena consisted of bilateral athetosis, marked generalized extrapyramidal muscular spasticity and mental retardation. The child died at the age of 3 years without demonstrable improvement in the neurologic or mental status. Necropsy revealed destruction of many of the cellular constituents of the caudate nuclei, putamina, cornua ammonis, substantia nigra and dentate, lateral thalamic and red nuclei. There was destruction of the cells and of the medullated nerve fibers of the pallida. The relationship of the pathologic changes in this case to those of kernikterus is discussed.

9. Vogt, C., and Vogt, O.: Zur Lehre der Erkrankungen des striären Systems, J. f. Psychol. u Neurol. **25**:531, 1920.

Progress in Pediatrics

FISTULA AURIS CONGENITA

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The term fistula auris congenita refers to a small sinus of the external ear, opening most commonly at the anterior border of the ascending limb of the helix (fig. 1). This aberration of development is of interest to the embryologist because of the different views that have been advanced concerning its origin. Its clinical significance lies in the fact that it can give rise to an offensive discharge, form a retention cyst or become infected. Infection of the fistula may result in a secondary lesion of the face in front of the ear which so dominates the clinical picture that the fistula itself may be overlooked. Prolonged, unsuccessful treatment of the secondary lesion through failure to recognize the relation of the lesion of the face to an aural fistula has been reported.

Fistula auris congenita was first described by Heusinger [1] in 1864. A voluminous German literature has since arisen. Grunert [2] gave references to many of the nineteenth century articles. More recent German articles are those of Schüller,[3] Seifert [4] and Zöllner.[5]

Paget [6] was the first of the English writers to describe the condition (1878). Kipp's [7] report was the first account of cases in this country. In 1932, Congdon, Rowhanavongse and Varamisara [8] published an article with a large number of photographs of fistulas of the ear. In

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1. Heusinger, K. F.: Hals-Kiemen-Fisteln von noch nicht beobachteter Form, Virchows Arch. f. path. Anat. **29**:358, 1864.

2. Grunert, C.: Zur Entstehung der Fistula auris und auriculae congenita, Arch. f. Ohrenh. **45**:10 (Sept. 20) 1898.

3. Schüller, J.: Zur Vererbung der Fistula auris bzw. auriculae congenita, München. med. Wchnschr. **76**:160 (Jan. 25) 1929.

4. Seifert, E.: Ueber die sogenannte Fistula auris congenita, Deutsche Ztschr. f. Chir. **209**:118, 1928.

5. Zöllner, F.: Fehldiagnosen, verursacht durch angeborene Fisteln und Cysten an Ohr und Hals, Ztschr. f. Hals-, Nasen- u. Ohrenh. **32**:54 (Sept.) 1932.

6. Paget, J.: Cases of Branchial Fistulae in the External Ears, Med. Chir. Tr. London **43**:41, 1878.

7. Kipp, C. J.: On Branchial Fistulae at the External Ear, Tr. Am. Otol. Soc. **2**:402 (July 21) 1880.

8. Congdon, E. D.; Rowhanavongse, S., and Varamisara, P.: Human Congenital Auricular and Juxta Auricular Fossae, Sinuses and Scars, Am. J. Anat. **51**:439 (Nov. 15) 1932.

addition to articles cited later are reports of cases by Amberg [9] and discussions on the subject by Binnie [10] and Keith.[11] Many of the otologic textbooks describe the condition.

The presence of the fistula is easily overlooked. Mothers of many of the children described in this study had been unaware of the presence of the fistulas in their children, and at times the mothers had not noticed that they themselves possessed fistulas. Seifert [4] reported the case of a colleague whose daughter had an aural fistula which had not been noted by the father. Mangakis [12] mentioned the case of a physician who had a fistula not observed until after his attention had been called to it by a previous article of Mangakis. In some of the cases reported in the literature the statement is made that the patient called the physician's attention to the abnormality, and as late as 1929 Schüller [3] remarked that the condition is not recognized by many physicians.

Fig. 1.—A well developed fistula of the common type, at the anterior margin of the helix. The antihelix points directly at it.

In the past few years I have examined 172 children with fistulas of the anterior margin of the helix. Because only a few references to this condition have been found in the pediatric literature (Erfurth,[13] Evans,[14]

9. Amberg: Congenital Aural Fistula, Physician & Surg. **35**:136 (March) 1913.

10. Binnie, J. F.: Remarks on Some Cases of Deformity of the External Ear, Ann. Surg. **24**:206, 1896.

11. Keith, A.: Three Demonstrations on Congenital Malformations of the Palate, Face and Neck, Brit. M. J. **2**:438, 1909.

12. Mangakis, M.: Cinq cas de fistules congénitales de l'oreille, Arch. internat. de laryngol. **34**:52, 1912.

13. Erfurth, W.: Zur Kasuistik der Ohrmissbildungen, Monatschr. f. Kinderh. **22**:55, 1922.

14. Evans, J. H.: (*a*) Case of Symmetrical Bilateral Branchial Fistulae with Symmetrical Bilateral Helical Fistulae and Misshapen Aural Pinnae, Rep. Soc. Study Dis. Child. **4**:114 (Jan. 19) 1904; (*b*) Auricular and Peri-Auricular Dermoids, Fistulae and Tumors of Congenital Origin, Brit. J. Child. Dis. **7**:490 (Nov.) 1910.

Gelston and Sappington [15] and Schwartz [16]) and because no report of the incidence of the condition in this country has been found, it has been thought advisable to present the observations made on these children.

FISTULA OF THE ANTERIOR MARGIN OF THE HELIX

While congenital fistulas occur in several sites in the external ear, by far the most common type is that found at the anterior margin of the ascending limb of the helix. In children the junction between the skin of the face and that reflected over the helix does not form a sharp fold or line of demarcation, so that precisely where the helix ends and the face begins may be difficult to determine. Nevertheless, in the children examined in the present study, as nearly as could be determined by looking down on the ear from above, the openings of the fistulas

Fig. 2.—A smaller marginal fistula.

appeared constantly to be in the skin of the helix rather than in that of the face. In the cases in which measurements were made, the horizontal distance from the center of the opening to the free posterior border of the ascending limb of the helix varied from 5 to 9 mm. and was most often from 6 to 7 mm.

The horizontal level of the opening was found to be about midway between the level at which the free portion of the helix begins and the level of the upper end of the tragus or sometimes a little above or below this level, but never as high as the free portion of the helix or as low as the tragus. In the majority of cases the line of direction of the antihelix passed exactly through the opening of the fistula; in the other cases the fistula was somewhat more often below than above this line.

15. Gelston, C. F., and Sappington, E.: Congenital Malformation of the Auricle Associated with Paralysis of the Facial Nerve, Arch. Pediat. **49**:730 (Nov.) 1932.

16. Schwartz, A. B.: Congenital Aural Fistula, Am. J. Dis. Child. **38**:1339 (Dec.) 1929.

Mouth of the Fistula.—The openings of the fistulas were never large, transverse diameters of 0.75 mm. or less being the general rule; a few fistulas were 1 mm. in width, 1.25 mm. being the greatest width recorded. Because of the oblique direction of the sinus, downward and inward, the openings tended toward the oval shape, and the vertical measurement was usually found to be greater than the transverse. A vertical measurement of 1 mm. or less was most common; 3 mm. was the greatest vertical measurement noted. While most often the openings had a roughly oval shape, with the lower and anterior border more sharply demarcated, at times a circular pit or a short, slitlike depression was encountered. The mouths of the sinuses were not built up but lay flat with the skin of the helix. At times the edges of the openings were clearcut, but frequently the presence of a yellowish material resembling sebum of the ear filled the opening. The black appearance of comedones was, however, lacking except in a few cases. Pressure from below upward to the mouth of the fistula sometimes succeeded in milking out a small drop of whitish fluid; at other times a thicker, caseous-like material was expressed. No instances were noted of hair protruding from the mouth of the fistula, although this might be expected from the histologic studies of other workers.

In some of the cases reported in this study, instead of a frank sinus admitting a probe, only a minute pit was present at the typical site of the fistula. The transverse and vertical measurements of the pits were smaller than those of frank sinuses. Still other cases presented a freckle at the typical site for fistulas, sometimes in association with a frank sinus of the other ear or in children whose siblings showed frank sinuses. These freckles were not included in the count of fistulas, but in certain cases they are undoubtedly substitutes for the fistula.

Direction and Length of the Fistula.—In fistulas examined with a probe the direction of the tract was found to be predominantly downward, slightly inward and often directed a little forward or backward. A more forward direction of the sinus tract was given by Evans,[14b] Kipp,[7] Paget,[6] Schüller,[3] Seifert,[4] Stammers,[17] Urbantschitsch[18] and Zöllner.[5] Lack of time and other circumstances did not permit the use of a probe in many of the cases reported in the present study. When the depth of the canal was measured, it was found to vary from almost nothing up to 7 mm. Congdon and his associates[8] reported few fistulas of more than 9 mm. in depth, but they pointed out that if the canal bends, a stiff probe may not reach the end of the canal. The injection of mate-

17. Stammers, F. A. R.: Pre-Auricular Fistulae, Brit. J. Surg. **14**:359 (Oct.) 1926.

18. Urbantschitsch, V.: Concerning the So-Called Fistula Auris Congenita, Monatschr. f. Ohrenh. **11**:85 (July) 1877; translation, Edinburgh M. J. **23**:690 (Feb.) 1878.

rial opaque to roentgen rays was suggested by Schüller.[3] Cases of rather long sinuses have been reported: Schüller [3] noted one of 22 mm. As some of the longer sinuses which were reported were infected, it may be questioned in these cases how much of the tract was of congenital origin and how much due to extension resulting from infection. By the use of probes, the injection of fluid or the study of extirpated tracts, various workers have found that the canal commonly ends blindly. In a few instances, presumably the result of infection, the canal has been reported to communicate with an ulcer, abscess or other fistulous opening.

Incidence.—A rather low incidence of aural fistulas is given in statistical reports of the frequency of various diseases of the ear, such as those of Bezold,[19] Bürckner [20] and Schubert.[21] However, Urbantsch-

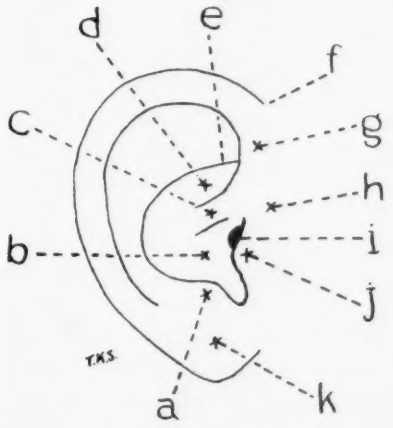

Fig. 3.—The normal ear of a child. The antitragus is indicated by *a*; the cavum conchae, by *b*; the crus of the helix by *c*; the cymba conchae, by *d*; the antihelix, by *e*; the beginning of the free portion of the helix, by *f*; the ascending limb of the helix, by *g*; the spine of the helix, by *h*; the external auditory meatus, by *i*; the tragus, by *j*, and the lobule, by *k*.

itsch [18] found 12 cases of fistulas among about 2,000 persons, and Onodi [22] 48 cases among 3,200 persons. In a study of oriental races, Congdon and his associates [8] found an incidence of 4 per cent in some racial stocks and 6 per cent in others.

In the present study 172 children with fistulas of the anterior margin of the helix are described. Of these, 34 were found in the routine

19. Bezold, F.: Gesammt. Bericht, Arch. f. Ohrenh. **21**:221 (Nov. 25) 1884.

20. Bürckner: Statistischer Bericht, Arch. f. Ohrenh. **44**:269 (June 30) 1898.

21. Schubert, P.: Bericht über das erste Lustrum ohrenärztlichen Thätigkeit, Arch. f. Ohrenh. **22**:51 (Feb. 5) 1885.

22. Onodi, S.: Ueber kongenitale Ohrfisteln, Arch. f. Ohren-, Nasen- u. Kehlkopfh. **102**:128 (April 26) 1918.

physical examination of 3,660 white children attending the schools of Hamilton County, outside Cincinnati, an incidence of 0.9 per cent. Two of the 34 children were siblings; the other 32 were from different families. Among the 1,865 boys there were 16 with fistulas, and among the 1,795 girls there were 18 with fistulas. Of 346 colored children examined in the Hamilton County schools, fistulas of the marginal type were found in 18, an incidence of 5.2 per cent. None of these 18 colored children were siblings. Of 180 colored boys 10 had fistulas, and of 166 colored girls 8 had fistulas. The difference between the white and the colored children is noteworthy.

Because of the possibility of the association of this condition with other graver abnormalities of development, the incidence of congenital aural fistulas in children attending the School for Crippled Children in Cincinnati was studied. Of 334 white children examined, only 4 were found to have fistulas of the marginal type. These 4 children had, respectively, poliomyelitis, Perthe's disease, scar contractures following burns and spastic paralysis following cerebral hemorrhage at birth, all of which were acquired rather than congenital developmental conditions. No instances of fistulas were found in 45 children who had defects of congenital origin as follows: congenital heart disease, 12; congenital clubfoot, 8; congenital deformity of the bones of the arms or legs, 6; spina bifida, 6; congenital dislocation of the hips, 2, and miscellaneous congenital conditions, 11.

In addition to the 34 white and 18 colored children in the county schools and the 4 in the School for Crippled Children, there were 116 children who had been found to have marginal fistulas since a special record of such cases was started a few years previous to the present writing. The number in the group from which these 116 cases were drawn is not known. The distribution of the total of 172 cases according to color, sex and the ear affected is shown in the tabulation.

	White		Colored		Total
	M	F	M	F	
Right	20	25	13	14	72
Left	20	17	9	15	61
Bilateral	10	12	7	10	39
					172

There were thus 39 cases of bilateral fistulas (22.7 per cent) and 133 cases of unilateral fistulas—72 of right-sided fistula and 61 of left-sided fistula—forming a total of 211 fistulas of the marginal type in 172 children. In the series of Portuguese workers cited by Fischer,[23] 1 of 45 cases presented a fistula of the right side only.

23. Fischer, H.: Considérations sur les fistules congénitales anté-auriculaires, J. de méd. de Bordeaux **106**:711 (Sept. 10) 1929.

Associated Conditions of the Ear.—One child of the series had chronic otitis media; another child had acute otitis media at the time of examination. Two children had accessory cartilage of the ear, and two presented gross deformity of the ear. In one of these children there were microtia, atresia of the external auditory canal and two fistulas, the larger one at the anterior margin of the helix and the smaller representing the canal. The other child had microtia, a normal external auditory canal, a typical marginal fistula and congenital paralysis of the facial nerve similar to that in the case reported by Gelston and Sappington.[15] Other cases of congenital fistulas in association with gross deformity of the ear were reported by Congdon and his associates,[5] Doran,[24] Grunert,[2] Hadda [25] and Sexton.[26]

Auricular Appendages.—The formation of accessory cartilage of the ear is another abnormality of development that is thought by some to be related to congenital aural fistula. The appearance of an auricular appendage in one member of a family and of fistulas in other members of the same family was reported by Ruttin;[27] he could find no report of the two conditions occurring in the same person. The possibility of such a familial relationship was not studied in the present series of children. I have noted auricular appendages much less frequently than aural fistulas. I usually found the appendages at the level of the spine of the helix or at the upper end of the tragus, below the typical position of the fistula. In one case, however, a child without an aural fistula was found to have three small cartilaginous nodules, the highest at the site for a marginal fistula, the second at about the spine of the helix and the third in front of the tragus. One of the 172 children with marginal fistulas had a fistula and accessory cartilage of the same ear, the cartilaginous nodule occupying the lower position. Another child had a nodule of the tragus on the same side as the fistula. Schüller [3] and Seifert [4] reported cases of a fistula and an auricular appendage in the same person.

Remains of Branchial Cleft in the Neck.—Fistula auris congenita was first described by Heusinger [1] because of its association with branchial fistulas of the neck. Other workers have since noted cases in which branchial remains in the neck and aural fistulas occurred

24. Doran, A.: Case of Congenital Auricular Sinus, Tr. Obst. Soc. London **33**:199 (June 3) 1891.

25. Hadda: Fistula auris congenita? Berl. klin. Wchnschr. **46**:711 (April 12) 1909.

26. Sexton, in discussion on Kipp.[7]

27. Ruttin, E.: Zur Frage der Fistula auris congenita und der Aurikularanhänge, Wien. med. Wchnschr. **77**:1019 (July 30) 1927.

together (Bull,[28] Evans,[4] Hamann,[29] Hyndman and Light,[30] Paget,[6] Schubert [21] and Urbantschitsch [18]). Levinstein [31] noted aural fistulas in a patient with a fistula of the left anterior pillar of the pharynx. However, in 51 cases of branchial cysts and fistulas of the neck, Shedden [32] noted only 1 case in which there was a dimple of the helix. None of the present series of 172 children with marginal helicine fistulas showed evidence of branchial remains in the neck. Among the 3,660 white children, 3 had no aural fistulas but branchial remains in the neck, as follows: One child had a thyroglossal cyst; 1 child had a cartilaginous nodule at the anterior border of the sternocleidomastoid muscle near the sternum, and 1 child had a cartilaginous nodule at the posterior border of the sternocleidomastoid muscle near its occipital insertion. Paget [6] and Sutton [33] described cartilaginous nodules of the neck.

Other Associated Abnormalities.—No cases of harelip or cleft palate were encountered among the 172 children with marginal fistulas. The conditions found in the 4 children of the School for Crippled Children with fistulas were noted in a preceding paragraph. One of the 172 children with fistulas had a tower head and nystagmus.

Minor abnormalities in the children with fistulas were as follows: 1 instance of incurved little fingers, 2 of an accessory nipple and several, usually in colored children, of rachitic hypoplasia of the teeth. Not all of the children with fistulas were given complete physical examination.

Ichthyosis was not found in any of the children with fistulas, but in three families siblings of children with fistulas had ichthyosis; this was possibly a chance association, as ichthyosis is relatively common.

The association of aural fistulas with other developmental disturbances aside from those of the ear and branchial system is rarely encountered in the literature. It would seem that disturbances in embryologic life affecting the branchial system or that part of it concerned with the formation of the external ear may give rise also to aural fistulas, but that the comparatively minor aberration of development resulting in aural fistulas does not often result in other changes in the body.

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28. Bull, Ole: Fistulae Fissurarum Branchialium, Arch. Otol. **17**:36, 1888.

29. Hamann, C. A.: Cases of Congenital Auricular and Cervical Fistulae, Cleveland M. Gaz. **9**:110 (Jan.) 1894.

30. Hyndman, O. R., and Light, G.: The Branchial Apparatus, Arch. Surg. **19**:410 (Sept.) 1929.

31. Levinstein, O.: Unvollständige innere Halskiemenfistel in Verbindung mit doppelseitiger Fistula preauricularis congenita, Arch. f. Laryng. u. Rhin. **23**:128, 1910.

32. Shedden, W. M.: Branchial Cysts and Fistulae, New England J. Med. **205**:800 (Oct. 22) 1931.

33. Sutton, J. Bland: On Branchial Fistulae, Cysts, Diverticula and Supernumerary Auricles, J. Anat. & Physiol. **21**:289 (Jan.) 1887.

Infection of the Fistula.—One child of the present series had an acute infection of the fistula, presenting an ear swollen and exquisitely tender at the ascending limb of the helix. Pus exuded from the opening of the fistula, from the inner side of the helix beneath and from a secondary ulcer of the face directly in front of the fistula. In another child with a marginal helicine fistula acute infection of the fistula was not evident, but a lesion of the face communicating with a second sinus leading to the external auditory canal was present; this lesion had been unsuccessfully treated by various measures, including roentgen treatment for four years, but was still present.

In the literature are other instances in which aural fistulas gave rise to pathologic symptoms (Andereya,[34] Cheatle,[35] Hamann,[29] Kipp,[7] Levinstein,[31] Lewis,[36] Morris,[37] Randall,[38] Rischbeith,[39] Schüller,[3] Schwabach,[40] Stammers,[17] Steiner,[41] Todd,[42] Urbantschitsch [18] and Zöllner [5]). In some of the cases reported there was a spontaneous discharge which was at times offensive in odor and at times irritated the skin about the mouth of the sinus. In a case reported by Rischbeith [39] there was a discharge only during the menstrual period. In other cases retention of the secretion and cyst formation caused pain. In cases of infection, pus escaped from the mouth of the fistula, or an abscess formed which spontaneously ruptured or discharged as a result of incision. Jacod's case [43] was possibly one of abscess of a fistula with no congenital opening.

At times the infection extended downward or forward, and an abscess was formed below or anterior to the opening of the fistula. Hamann [29] reported a case of fistula with suppuration of the preauricular lymph nodes. Possibly in some of the other cases with preauricular lesions adenitis of the anterior auricular lymph nodes secondary to an infection

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34. Andereya: Doppelseitige Fistula auris congenita, Deutsche med. Wchnschr. **33**:283 (Feb. 14) 1907.

35. Cheatle, in discussion on Tilley.[46]

36. Lewis, F. P.: A Peculiar Inherited Ear Mark: Fistula Auris Congenita, J. Ophth., Otol. & Laryng. **3**:14, 1891.

37. Morris, R. T.: A Case of Congenital Fistula of the Ear, New York M. Monthly **1**:169 (March) 1887.

38. Randall, B. A.: Some Cases of Supernumerary Auricle and Congenital Aural Fistula, Tr. Am. Otol. Soc. **4**:485 (July 16) 1889.

39. Rischbeith, H.: Congenital Auricular Fistula, M. J. Australia **2**:251 (Sept. 23) 1916.

40. Schwabach, D.: On Branchial Fistulae at the External Ear, Arch. Otol. **8**: 246, 1879.

41. Steiner, A.: Zwei Fälle von Fistulae auris congenitae, Dermat. Wchnschr. **86**:325 (March 10) 1928.

42. Todd, C. A.: Anomalous Sebaceous Gland in Immediate Proximity to the Auricle, Tr. Am. Otol. Soc. **3**:109, 1883.

43. Jacod, M.: Fibrochondrome branchial pré-auriculaire fistulisé, Lyon méd. **151**:613 (May 14) 1933.

of the fistula rather than a direct extension from the fistula itself may have been responsible for the lesions on the face. The anterior auricular lymph nodes are described in Gray's "Anatomy" as lying just in front of the tragus. In some of the cases of secondary lesions in the literature, long sinuses reaching from the mouth of the congenital fistula to the lesion itself are described. In view of the usual short length of the congenital sinuses, it would seem possible that the part of the fistulous tract contributed by developmental abnormality in these cases was relatively short, and that infection created a new fistulous tract continuous with the original one.

Whatever the origin of the preauricular lesions, once present they may become chronic and exist for months or years as recurrent abscesses, rupturing or being incised and healing over, only to form again, or they may persist as chronic ulcers. Sometimes there is healing with the persistence of a preauricular sinus which may be mistaken for a sinus of congenital origin.

Several of the children with fistulas presented scars of the ear and face in the immediate neighborhood. Whether any of the scars resulted from infection of the fistulas could not be determined from examination alone. One child with a typical fistula had an infant brother with a small scar at about the spine of the helix which the mother stated had been present from birth. This may be an example of the congenital scars mentioned by Congdon and his associates.[8]

Hereditary Tendency.—The hereditary nature of aural fistulas has been noted by many workers, including Hamann,[29] Hyndman and Light,[30] Kipp,[7] Lewis,[36] Montgomery,[44] Paget,[6] Rischbeith,[39] Rugani,[45] Schubert,[21] Schüller,[3] Schwabach,[40] Stammer,[17] Tilley,[46] Todd[42] and Urbantschitsch.[18] The abnormality is transmitted by both father and mother. Schüller[3] studied the occurrence of the condition in a large family, and Lewis[36] reported its existence in four generations. In the children of the present study the hereditary nature of the fistula was likewise noted; several of the parents were found to have fistulas. The number of cases in which more than 1 child in a family was affected, however, was not so large as the selected reports in the literature would lead one to expect. As many as possible of the siblings of children with fistulas were examined, but only 17 instances were noted in which more than 1 child in the family had fistulas of the margin of the helix. In another family 1 child had a marginal fistula, and a sister had bilateral

44. Montgomery, M. L.: Congenital Auricular Fistula, S. Clin. North America **11**:141 (Feb.) 1931.

45. Rugani, L.: De la fistule auriculaire congénitale, Arch. internat. de laryng. **29**:119, 1910.

46. Tilley, H.: A Child with Congenital Abnormalities of Both Ears, Tr. Otol. Soc. U. Kingdom **1**:39, 1900.

fistulas of the crus of the helix. In a few other instances the history was given of another child, not examined, who had a marginal fistula. No instances were noted in which more than 2 children in the same family were found on examination to have fistulas.

Histologic Examination.—Sections of fistulas were not studied in any of the cases reported in the present study. Reports of Congdon and his associates,[8] Grunert,[2] Seifert,[4] Stammer,[17] Steiner [41] and Zöllner [5] on the structure of marginal fistulas indicated that the sinus is lined not with mucous membrane but with normal skin which carries sheaths of hair and sweat and sebaceous glands. The glandular elements are sometimes enlarged through retention, and at times one or another of the accessory cutaneous structures is lacking.

Embryology.—Discussions of the embryology of aural fistulas has occupied a large part of the literature on this condition because of the earlier view that they are the result of imperfect closure of the first branchial cleft and the later view that they are the result of a failure of fusion of the six primitive tubercles grouped about the first branchial cleft from which the pinna is formed. Still other views have been advanced, and the question cannot be said to be satisfactorily settled. It may be stated here that the commonly used term "disturbance of development" suggests an extraneous factor, whereas an event which takes place so often in certain families must be thought of in terms of hereditary rather than accidental influences. Federici [47] and Congdon and his co-workers [8] recently gave discussions on the subject.

Treatment.—Usually the sinuses cause no trouble and are let alone. Relief may be sought because of the presence of an offensive or irritating discharge or because of pain from the retention of secretion. At other times the presence of a frank abscess or ulcer may be the presenting symptom. In some of the cases in the literature preauricular lesions secondary to infection of the fistulas so dominated the clinical picture that the presence of the fistula itself was overlooked. Long-continued treatment by cautery, curettage, ultraviolet rays from a quartz mercury vapor arc lamp, roentgen rays, tuberculin and other measures has been noted in such cases. Excision of the fistula resulted in healing in most of the cases reported but not in all (Steiner [41]). In 1 of the cases in the present study excision of the congenital fistula resulted in healing, and in another case excision of a fistulous tract leading away from the preauricular lesion, leaving the congenital sinus itself, likewise resulted in healing. In a case reported by Cheatle,[35] splitting of the sinus tract without excision was done. Spontaneous healing without excision took place in cases noted by Schüller.[3] In cases of spontaneous healing there is the possibility of sealing up a tract bearing hair and other epidermal

47. Federici, F.: De l'interprétation embryologique de la "fistula preauricularis congenita," Acta oto-laryng. **14**:532, 1930.

structures. Evans [14b] noted that the site of the marginal helicine fistula is a common one for dermoid cysts of the pinna. Except for this, the question of a relation between congenital fistulas and new growth of the auricle has not been mentioned in the literature surveyed. When there is a long sinus, whether this is made up of a congenital tract or the extension of a congenital tract through infection, the possibility must be kept in mind of deformity of the ear resulting from an extensive excision.

OTHER TYPES OF AURAL FISTULAS

Congenital fistulas of the ear other than those of the anterior margin of the helix are sometimes found, although they occur far less frequently.

Crural Fistulas.—The crural type of fistula is found opening in about the middle of the lateral wall of the crus of the helix (fig. 4). Eight

Fig. 4.—A crural fistula in the middle of the lateral wall of the crus of the helix. This type is much less common than the marginal type.

examples of this type of fistula were seen within the period of time during which the 172 cases of fistula of the margin of the helix were recorded, 3 in white and 5 in colored children. In 1 of the 8 cases a fistula of the anterior margin of the helix was present in one ear, and a fistula in the crus was found in the other ear. In another case of crural fistula a sibling had a marginal helicine fistula. The incidence of crural fistulas was as follows: Among the 3,660 white school children, there were 2 with crural fistulas but no marginal fistula, and among the 346 colored school children there was the aforementioned case in which there were a crural fistula of one ear and a marginal fistula of the other, and 1 case of crural fistula alone. Two of the eight children had bilateral crural fistulas. This type of fistula was mentioned by Schwabach [40] and described with photographs by Congdon and his associates.[8]

One child with bilateral marginal fistulas had, in addition, in one ear a fistula in the helix situated at about the junction of the crus and the ascending portion of the helix, midway between the sites for the marginal and crural fistulas; this type of fistula was also mentioned by Congdon and his associates.[8]

Superior Posterior Helicine Fistulas.—A fistula of the helix at its superior, posterior portion (fig. 5) was noted in a few cases, but its frequency is a matter of doubt, as it was not looked for as a routine. In the cases observed the fistula was shallow. Reference to this type of fistula is found in the article of Congdon and his co-workers.[8]

Lobular Fistulas.—I have noticed several instances of pits of the external aspect of the lobule similar to those described by Jenks;[48] they varied from just barely visible to well marked linear depressions. In

Fig. 5.—Fistula of the superior posterior portion of the helix.

one child of the present study with bilateral fistulas of the margin of the helix a deep pit was found on the inner side of the lobule at its junction with the eminentia conchae, more marked in the one ear than in the other. Cases of fistulas of the lobule have been reported by Breuer,[49] Fischer,[50] Meyer [51] and Sutton.[33] References to still other cases are given in their articles.

Fistulas of the Conchae.—A number of children with openings in the cavum conchae and cymba conchae were observed, but as these locations are favorite sites for comedones, it was questioned whether the

48. Jenks, A. E.: Pitted Ear Lobes of Congenital Origin, J. Hered. **7**:553 (Dec.) 1916.

49. Breuer, F.: Ueber Fistula auriculae congenita, Deutsche Ztschr. f. Chir. **202**:278 (May) 1927.

50. Fischer, H.: Fistel am Ohrläppchen links, Arch. f. klin. Chir. **69**:263, 1903.

51. Meyer, W. H.: Congenital Cysts and Fistulae of the Neck, Ann. Surg. **95**:13 (Jan.) 1932, fig. 15.

openings were those of true congenital fistulas. However, a fossa of congenital origin is frequently encountered in children just above and posterior to the external auditory meatus, between the meatus and the crus, with at times a linear depression reaching from it down to the external meatus. Fistulas in the neighborhood of the external meatus simulating a double auricular canal have been reported by Habermann,[52] Spira [53] and others.

Postauricular Fistulas.—Fistulas of the postauricular region have been recorded by Battle,[54] Hadda,[25] McKenzie,[55] Moldenhauer [56] and Zöllner.[5] In most of these cases the fistulas were apparently secondary to infection rather than due to developmental errors. In Zöllner's case [5] the postauricular fistula communicated with a marginal helicine fistula.

Preauricular Fistulas.—The term preauricular or anteauricular has been used at times (Federici,[47] Fischer,[23] Levinstein,[31] Seifert [4] and Stammers [17]) unequivocally to denote the marginal helicine type of fistula. At other times, however, it is evident that the term refers to a fistula of the face definitely away from the ear. In a case reported by Schüller [3] formation of an abscess from a helicine fistula was followed by the appearance of 2 preauricular fistulas. Hadda's [25] case of imperforate meatus appears to have been due to infection. Jacod's [43] case followed the formation of an abscess. Fistulas on the helix with more anterior preauricular fistulas have been reported by Barrett,[57] Congdon and others,[8] Montgomery [44] and Schwabach.[40] Cases of preauricular fistulas accompanied by scars have been reported by Congdon and others.[8] A few cases, however, of preauricular fistulas without marginal fistulas or scars have been noted; thus Pflüger [58] reported one which was 7 mm. anterior to the helix and Urbantschitsch,[18] one which was 6 mm. anterior to the helix. Since infection can give rise to preauricular fistulas and evidence of infection has been present in most cases, it would seem that commonly an infectious rather than a developmental origin must be

52. Habermann: Ueber Verdopplung des äusseren Gehörganges, Arch. f. Ohrenh. **50**:102 (Sept. 20) 1900.

53. Spira, R.: Seltener Fall einer kombinierten angeborenen Missbildung des äusseren Gehörganges, Monatschr. f. Ohrenh. **41**:664, 1907.

54. Battle, W. H.: A Case of Post-Auricular Fistula, Tr. Clin. Soc. London **39**:248, 1906.

55. McKenzie, D.: Congenital Redundant External Meatus, Brit. J. Child. Dis. **17**:30 (Jan.-March) 1920.

56. Moldenhauer, W.: Die Missbildungen des menschlichen Ohres, in Schwartze, H.: Handbuch der Ohrenheilkunde, Leipzig, F. C. W. Vogel, 1892, vol. 1, p. 154.

57. Barrett, J. H. P. B.: Congenital Fistulae, Dublin J. M. Sc. **131**:179 (March) 1911.

58. Pflüger: Ein Fall von Fistula auris congenita, Monatschr. f. Ohrenh. **8**: 131 (Nov.) 1874.

ascribed to this type of fistula. Rupture of a cyst without infection is also a possible origin.

Miscellaneous Types of Fistulas.—Cases of a double opening, one in the neck and the other in the ear, have been reported by König [59] and Küttner.[60]

The record of a fistula of the antitragus has been ascribed to Dyer.[61] This was a case of fistula of the ear reported in the minutes of a medical society meeting, and it appears that the heading "Fistula of the Antitragus" was a typographical error, as the details of the description do not agree with the heading. Furthermore, in another report of Dyer,[62] obviously of the same case, the fistula was described as being in the tragus.

REPORT OF CASES

CASE 1.—R. A., a white boy, aged 6 years, one of the 3,660 white school children, had a fistula in the middle of the lateral wall of the crus of the helix on the right side. There was no fistula of the left ear.

CASE 2.—D. A., a colored girl, aged 5 years, one of the 346 colored school children, had a fistula at the anterior margin of the ascending limb of the helix of the right ear and a fistula of the crus of the helix of the left ear. There were no other children in the family. The mother had bilateral marginal helicine fistulas.

CASE 3.—G. B., a white boy, aged 11 years, one of the 3,660 white children, had a left-sided fistula of the common marginal type. H. B., his brother, aged 1 year, who was seen at a clinic, also had a left marginal fistula. Both boys had normal skin. Three siblings had ichthyosis but no fistulas; another was free from fistula and ichthyosis; 2 siblings were not examined.

CASE 4.—C. B., a white girl, aged 11 years, was seen at the outpatient department of the Children's Hospital. There was a history of the appearance of an abscess in front of the right ear four years previously; the abscess was operated on, but it did not heal. The patient had received roentgen treatments two years previously. There were repeated swelling and spontaneous rupture. Examination showed what appeared to be a chronic ulcer of the face immediately in front of the right ear and congenital fistulas at the anterior margin of the ears, but no discharge from the fistulas. Operation by a member of the surgical service showed a long sinus tract reaching from the ulcer to the external auditory canal near the drum, which was excised. Reexamination four years later showed a good cosmetic effect with a smooth scar measuring about 2 by 3 cm., the posterior border touching the ascending limb of the helix just below the mouth of the congenital fistula, its main portion lying immediately in front of the ear above the zygomatic arch and its inferior border overlapping the arch. The congenital fistula of this ear was still present but shallow. One possibility was that the infection originated in the marginal fistula, and that the tract became obliterated when

59. König, F.: Ueber Fistula colli congenita, Arch. f. klin. Chir. **51**:578, 1896.

60. Küttner, H.: Die Hyomandibularfistel, eine neue Form der angeborenen Halsfistel, Deutsche med. Wchnschr. **39**:489 (March 13) 1913.

61. Dyer, E.: Fistula of the Antitragus, M. News **46**:24 (Jan. 3) 1885.

62. Dyer, E.: Fistula Auris, Tr. Am. Otol. Soc. **3**:468, 1885.

drainage through the abscess in front of it became established. Whether the sinus tract leading to the external auditory canal was a congenital sinus or one created by the infection could not be determined. The left ear, in addition to a marginal fistula, had a second fistula on the helix at about the junction of the crus and the ascending limb, midway between the typical sites for crural and marginal fistulas, an intermediate type of fistula.

CASE 5.—E. D., a white girl, aged 7 years, was seen in the pediatric service of the Jewish Hospital, with an infection of the helix and of the face in front of the left ear. Two months previously a small furuncle had appeared on the outside of the ear and rapidly increased in size. Four weeks previously it had ruptured and discharged pus; this had been repeated a number of times. On examination, pus was found exuding from the inner surface of the ascending limb of the helix of the left ear; the outer surface was covered with a crust obscuring the site at which a fistula auris congenita was found. Anterior to the ear in the skin of the face, above the zygomatic arch, was an ulcer discharging pus. After the crust on the outer surface of the helix had been cleaned off, a fistula was found in the typical site with pus exuding from its mouth. The sinus tract was excised in the otologic service.

CASE 6.—J. D., a colored girl, aged 12 years, had right and left fistulas of the crus of the helix. One brother, aged 7 years, had a right-sided fistula of the marginal type. Neither of two siblings had a fistula. Four siblings were not examined. The mother had no fistula.

CASE 7.—R. F., a colored girl, aged 4 years, had a marginal fistula of the right ear and a small cartilaginous nodule in, not anterior to, the right tragus; it was not raised so much as a typical auricular appendage.

CASE 8.—P. H., a colored girl, aged 9 years, had a fistula of the crus of the right helix, but no fistula of the left ear. Five siblings had no fistulas. A sixth sibling was not examined. The mother had no fistula.

CASE 9.—E. H., a white girl, aged 12 years, had a fistula of the crus of the right helix. It was not exactly in the middle of the lateral wall, but a little toward the superior surface of the crus. The opening was 1 mm. in height and 1.5 mm. in length. One sister had a well marked fossa of the cavum conchae between the meatus and the crus, just above and posterior to the meatus. Another sibling had no fistula, and one sibling was not examined.

CASE 10.—H. H., a colored girl, aged 4 months, had bilateral fistulas of the crus of the helix. A twin had no fistula. Three other siblings had no fistulas. One sibling was not examined.

CASE 11.—L. K., a colored boy, aged 7 years, had a right marginal fistula which was less than 0.5 mm. in diameter and which admitted a fine probe for a distance of 2 mm. Nystagmus occurred when the patient looked to one side; there were an apparent bony defect at the site of the left frontal boss, tower head with excessive height of the frontal bone and steep parietal bones. Two siblings were normal. The mother had no fistula.

CASE 12.—L. L., a white boy, aged 7 years, one of the 3,660 white children, had a typical left marginal fistula. The skin was normal. One sibling showed definite ichthyosis but no fistula. Two siblings were normal. Four siblings were not examined.

CASE 13.—E. N., a white boy, aged 6 years, one of the 3,660 white children, had a fistula of the crus of the right helix.

CASE 14.—R. R., a white girl, aged 7 years, had marginal fistulas of the right and left ears. In addition, there was a well marked pit measuring 1 by 1.5 mm. on the cranial surface of the lobule of the right ear at the junction of the lobule with the eminentia conchae. There was a definite but less marked pit of the left lobule in the same position.

CASE 15.—E. S., a white girl, aged 11 years, had a fistula of the anterior margin of the helix of the left ear. Below, just anterior to the upper end of the tragus, was a well defined nodule representing an auricular appendage, not pedunculated or so elevated as in typical pictures in textbooks. One sister had neither a fistula nor an auricular appendage. There were no other children in the family.

CASE 16.—E. V., a colored girl, aged 7 years, one of the 346 colored children, had a fistula of the crus of the helix of the left ear. There was no marginal fistula. There were no other children in the family.

CASE 17.—E. W., a white girl, aged 8 years, had a right ear of normal size but turned forward markedly, and the ascending limb of the helix was scarred. The left ear showed microtia; the canal of the ear and drum were normal; there was typical fistula at the anterior margin of the ascending limb of the helix. There was left facial paralysis involving the forehead, eye and cheek. There was a history obtained from an older sister of paralysis from birth and of "operation" on the right ear. One sister had bilateral marginal fistulas. There were no other children in the family.

CASE 18.—G. W., a white girl, aged 13 years, one of the series of 3,660 white children, had microtia on the right side, a small fistula measuring about 0.5 mm. in diameter and representing the rudimentary external auditory meatus and a fistula measuring 1 by 1.5 mm. at the typical site for marginal fistula. The patient had rheumatic heart disease; the skin was normal. One brother had definite ichthyosis but no fistula. The third child had a normal skin but no fistula. Three siblings were not examined.

SUMMARY

Congenital fistula of the external ear at the anterior margin of the ascending limb of the helix is a comparatively common but easily overlooked peculiarity.

Thirty-four (0.9 per cent) of 3,660 white school children and 18 (5.2 per cent) of 346 colored school children were found to have this type of fistula.

In the past few years 120 other children with fistulas at the anterior margin of the helix, making a total of 172, have been examined.

A fistula of the crus of the helix was found in 8 children during the same period of time.

Other types of aural fistulas are discussed.

Congenital fistulas of the ear usually are found in otherwise normal children, but sometimes in association with other abnormalities of the ear or with branchial remains in the neck.

Infection of a congenital fistula can give rise to a lesion of the fistula itself or of the face in front of the ear. The latter may be unsuccessfully treated unless its origin in the congenital fistula is recognized.

CYST OF THE LARYNX IN INFANCY

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Cyst of the larynx in infancy is rare. A thorough search of the literature revealed only eleven cases recorded prior to ours. In none of the textbooks on pediatrics is any mention made of this condition as a possible cause of asphyxia at birth or in early infancy. Still more infrequent is cyst involving the epiglottis of the new-born. So far as our search of the literature revealed, only one case is on record.

Park and Israel [1] sent questionnaires to approximately one hundred and fifty pediatricians and otolaryngologists throughout the United States requesting a statement as to their experience with laryngeal cysts in infancy and childhood. Most of the replies were to the effect that the physician had never seen a case in infancy or childhood. Chevalier Jackson, who has probably had the widest experience, stated that the earliest case he had seen was in a child of 13 months.

The first recorded case of laryngeal cyst in infancy was presented in 1876 by Edis [2] before the London Obstetrical Society. Subsequent records have been made by Horne [3] (1898), Porak and Theuvernay [4] (1902), Mix [5] (1907), Saloman [6] (1910), Stoerck [7] (1916), Chamber-

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From the Department of Pathology of the Beth-El Hospital and the Office of the Chief Medical Examiner of New York City, Dr. Charles Norris.

1. Park, J. H., and Israel, S.: South. M. J. **18**:128 (Feb.) 1925.
2. Edis, J.: Tr. Obst. Soc. London **18**:2, 1876.
3. Horne, J.: J. Laryng. & Otol. **3**:65, 1898.
4. Porak, C., and Theuvernay, E.: Compt. rend. Soc. d'obst., de gynéc. et de pædiat. de Paris **4**:150, 1902.
5. Mix, quoted by Greene, D. C.: Laryngoscope **17**:800, 1907.
6. Saloman, W.: Ztschr. f. Ohrenh. **62**:49, 1910.
7. Stoerck, O.: Frankfurt. Ztschr. f. Path. **19**:149, 1916.

lin [8] (1917), Pünder [9] (1918), Park and Israel [1] (1925), Rosenberger [10] (1927), Lorie and Lux [11] (1932) and Myerson [12] (1933).

ETIOLOGY AND PATHOLOGY

Cysts of the larynx may have one of several sources of origin, the most common being the closure of a mucous gland resulting in the formation of a retention cyst (Brindel [13] and Oppikofer [14]). Jurasz [15] explained this comparative frequency as due to the fact that fragments of saliva and other materials may be jammed into a mucosal gland during the act of swallowing, with resultant occlusion and formation of a retention cyst.

Other causes may be embryonic maldevelopment (Senator [16]), inclusion of squamous epithelium (Kahler [17] and Duverney [18]), distention of blood vessels and lymph channels (Chiari [19]) and dermoid cysts (Blanc [20] and Pinsiegle [18]). Park and Israel [1] held that traumatism incidental to labor may also cause the formation of a cyst.

Recently there have come to our attention two cases of cyst of the larynx and epiglottis in infancy.

REPORT OF CASES

CASE 1.—Renee A., aged 10 weeks, was admitted to the general pediatric service on Aug. 7, 1932, with a history of attacks of difficult breathing since birth.

The infant was born at full term, with a face presentation, delivery being effected by the aid of midforceps. The weight at birth was 5 pounds and 10 ounces (2,551.5 Gm.).

Pyonephrosis subsequently developed in the mother, and the infant was fed with a modified cow's milk formula.

Shortly after birth the child had attacks of dyspnea accompanied by cyanosis and a peculiar shrill cry. The head was extended, which seemed to lessen the dyspnea, for when flexion was attempted the breathing became labored and cyanosis intervened once more. The child took her feedings well and for a while gained

8. Chamberlin, W. B.: Laryngoscope **27**:622, 1917.
9. Pünder, A.: Jahrb. f. Kinderh. **87**:65, 1918.
10. Rosenberger, H. C.: Laryngoscope **37**:360, 1927.
11. Lorie, A. J., and Lux, P.: Laryngoscope **42**:957, 1932.
12. Myerson, M. C.: Cysts of the Larynx, Arch. Otolaryng. **18**:281 (Sept.) 1933.
13. Brindel, A.: Rev. hebd. de laryng. **17**:161, 1897.
14. Oppikofer, A.: Arch. f. Laryng. u. Rhin. **21**:385, 1908-1909.
15. Jurasz, A., in Heymann, P.: Handbuch der Laryngologie und Rhinologie, Vienna, A. Hölder, 1898, p. 826.
16. Senator, M.: Deutsche med. Wchnschr. **10**:173, 1902.
17. Kahler, O.: Arch. f. Laryng. **17**:11, 1905.
18. Duverney, J. G.: Quoted by Pinsiegle: Etude sur les tumeurs de l'epiglotte, Thèse de Lyon, 1905.
19. Chiari, O., quoted by Park and Israel.[1]
20. Blanc, E.: Rev. mens. de laryng., d'otol. et de rhinol. **3**:324, 1883.

slowly but steadily. During the ten weeks prior to her admittance she was seen by several doctors and at several clinics, where various diagnoses of tracheitis, enlarged thymus and cerebral hemorrhage were made. As time went by, the signs became more intense, and hospitalization was advised.

Physical examination revealed a well developed, poorly nourished white female infant, lying in bed with the head in marked retraction. Breathing was labored, causing the child to use her accessory muscles, pulling in the sternum, so that a deep funnel-shaped depression was produced. A prominence of the soft tissue in the left submaxillary region was present, which felt cystic. The skin over the face was dry and drawn. The anterior fontanel was widened, depressed and tautly drawn. The tongue was swollen and coarsely granular in appearance. A peculiar shrill cry was noted.

The heart, lungs and abdomen were normal. The reflexes were present and active. The temperature on admission was 100 F. The urine was normal, and the blood showed mild secondary anemia.

Roentgen examination of the chest revealed a widening of the superior mediastinal shadow.

A diagnosis of natal injury to the muscles of the neck and to the larynx was made.

The day following this examination the child was seen by the laryngologist, who felt that the larynx was displaced. Laryngoscopy was not advised, but replacement of the larynx through an external operation was contemplated.

During that day the temperature was 103 F. and the respirations were 118 per minute. At night the intern was called and found the infant dead.

Postmortem Examination.—The body was that of a poorly nourished white female infant, aged 10 weeks, weighing 7½ pounds (3,401 Gm.) and measuring 24 inches (61 cm.) in length.

The eyes were sunken. The skin was dry and hanging in loose folds. The scalp covering the anterior fontanel was taut and depressed.

Examination of the head showed no free blood or fluid in the cranial cavity. The cerebral vessels were markedly congested. There was no disturbance in the structure of the brain.

Examination of the neck revealed a thyroid gland weighing 3 Gm. On dissecting the skin of the neck from the underlying tissue there appeared a bulge on the left side of the neck beneath the sternomastoid, the sternothyroid and sternohyoid muscles extending laterally outward and somewhat backward for a distance of 6 cm., the direction of the extension being at an angle of 45 degrees from the sagittal plane of the tongue and trachea. This entire area was composed of thin-walled translucent cysts varying in size from 3 mm. to 2 cm. The outer surface of these cysts was smooth and dull grayish white; it could be easily separated from the adjacent connective tissue and the overlying muscles. The cysts lay immediately adjacent to the outer laryngeal wall. The cysts were apparently in communication, for when one was opened the neighboring cysts seemed to shrink and the fluid entered the evacuated cyst. The content of the cysts was a clear colorless odorless fluid, which was negative to the guaiac and benzidine tests. It showed no cells microscopically. The inner lining of the cysts was shiny and glistening. Overlying the left side of the epiglottis and extending from its apex to its base on this side was a cystic bulge, 1.2 by 0.9 by 0.7 cm., which extended out to the pyriform fossa. It pushed the left epiglottic wall sharply to the right and into the laryngeal vestibule. When the head was flexed on the chest, the epiglottis completely occluded the entrance to the larynx. When the head was sharply extended and turned toward the left, the opening was patent.

The cyst lay beneath the mucosa of the base of the tongue and the lateral epiglottic wall and pyriform fossa. Its outer surface was dull and slightly corrugated, like that of the other cysts, and was apparently continuous with the covering of these structures. The cyst was filled with about 0.6 cc. of a fluid similar to that found in the other cysts (fig. 1).

The body of the sternum presented marked concavity extending from the level of the third to that of the sixth costal cartilage. There was no free blood or fluid in the pleural cavities. The left lung was smaller than the right, the former

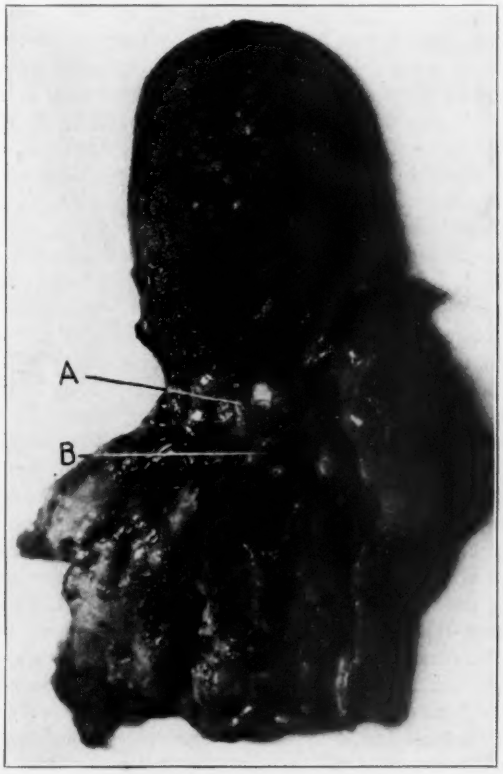

Fig. 1 (case 1).—Posterior view of the trachea showing a cyst in the left lateral epiglottic wall. *A* denotes the unopened cyst in the epiglottic wall, and *B*, the left aryepiglottic fold.

showing atelectasis along the paravertebral border. The right ventricle was dilated and filled with a dark red blood clot. The valves and cusps were intact.

The abdominal organs were normal on gross examination.

Microscopic Examination.—Sections through the epiglottic region to include the cyst as well as seriatim sections through the larynx and esophagus and the surrounding fibromuscular tissue as far as the lower border of the thyroid cartilage presented essentially the same appearances. The esophageal, laryngeal, epiglottic and pharyngeal mucosa showed normal histologic structure. In the extrinsic fibromuscular tissue were numerous cystlike spaces, many collapsed and empty

and with their surfaces apposed; others—and these were chiefly near the large para-epiglottic cystic area grossly described—were distended with homogeneous slightly vacuolated or shredded pale acidic substance, without cellular or nuclear structure and resembling the edematous fluid of the lungs. Here and there in the periphery of such contents were a small number of poorly outlined swollen oval cells (endothelial cells) measuring 20 microns, each showing a large central vesicular nucleus that was finely granular, faintly outlined and sparsely chromatic, and without a demonstrable nucleolus. Scattered irregularly throughout the contents of the cysts were moderate numbers of lymphocytes. No erythrocytes and no fibrin were demonstrable in the contents of the cysts.

The large para-epiglottic cyst lay close to the epithelial linings of the pharyngeal wall and the lateral wall of the epiglottis but was separated from each by a zone of dense and acellular elastic tissue. The cyst was incompletely lined by a single layer of endothelial cells with flattened and elongated nuclei, poorly chromatic and without demonstrable nucleoli but with fairly well defined outlines. These cells resembled those found in the intracystic contents; in places they were swollen, projecting slightly into the lumen of the cyst, generally near a group of desquamated cells. These lining cells rested directly on a narrow zone of fine fibrillar connective tissue in which an occasional elongated connective tissue cell was present. The fibrils took a faintly pink color with the Van Gieson stain and were arranged more or less parallel in a delicate reticulum to the cells lining the cyst. There was no adult connective tissue or blood vessels in this zone. It passed without demarcation into a zone stained pink or pink-red with Van Gieson stain. While still arranged more or less parallel to the surface layer of the cyst, this zone showed a coarser reticular meshwork interrupted by numerous short and rather delicate wavy elastic tissue fibrils. These, generally discontinuous, were arranged strictly parallel to the lining of the cyst, even into the short and stubby papillary lining folds. In this layer were moderate numbers of well formed capillaries and a few venules and arterioles, all showing normal histologic structure and somewhat more numerous connective tissue cells. The reticulum became somewhat less marked, and the elastic tissue fibrils were coarser and longer and showed a tendency to become grouped. Finally, in the surrounding zone, a narrower one than the preceding zone, there were long coarse elastic tissue fibers, generally straight, densely packed but without definite lamellar formation; this zone was completely avascular and acellular, and with only a scant interfibril or fine collagenous reticulum without definite direction. All of the elastic tissue fibers were arranged parallel to the lining of the wall of the cyst. This zone was immediately surrounded by, and was the definable demarcating zone of, cyst wall, dense connective tissue separating the cyst from the overlying submucosal stroma of the laryngeal epiglottic and para-esophageal wall. It was also present, though narrower and less well defined, around the cysts present in the intermuscular fascial tissue.

The description of the histologic character of the large cyst obtains as well for the smaller cysts whether they were dilated or collapsed. The majority of the smaller cysts were present around the pretracheal and prelaryngeal fascial septums, but occasional cysts were also seen in the fibrous tissue septums of the intermuscular bundles; the latter were minute. Groups of neighboring cysts apparently communicated; all of a group were either collapsed or dilated. No extrusion of a cyst into a laryngeal, tracheal or esophageal lumen, no ciliated epithelial lining in a cyst wall, no residual branchial cleft tissue was apparent in any section; nor could points of fibrosis around, or occlusion of, the cysts be demonstrated.

Except for the alterations described, all of the cervical organs and tissues showed normal histologic and cytologic characteristics.

The lungs showed widespread atelectatic areas with an occasional ruptured alveolar septum. These emphysematous patches were most frequent in the subpleural zones. All of the capillaries of the alveolar and bronchial walls were markedly congested, as were the pulmonary arterioles.

The heart, liver, kidneys and spleen showed a pronounced venous and capillary congestion. The cysts were apparently of lymphangiectatic type.

CASE 2.—The patient was a new-born female infant delivered spontaneously at Harlem Hospital on Dec. 4, 1932. The mother's past history and physical condition at the time of the child's birth were irrelevant.

Fig. 2 (case 2).—Posterior view of the unopened trachea showing the cyst in the right lateral epiglottic wall. *A* denotes the unopened cyst.

Shortly after birth it was noted that the child's respiratory efforts were exaggerated. The cry was hoarse and feeble. Cyanosis was present.

Physical examination of the chest revealed prolonged expiration and inspiration, but no râles were heard. The heart sounds were normal.

In spite of hypodermic and manual stimulation, the child died of asphyxia six hours later.

Autopsy.—The body was that of a white new-born female infant, weighing 6 pounds (2,721.6 Gm.), showing marked cyanosis of the entire body and oral

mucous membranes, but not otherwise externally remarkable. A bulge displacing the epiglottis toward the left was visible when the head was retracted and one looked down toward the larynx. With the head in this position, even with the epiglottis pulled downward, the rima glottidis appeared as a slit only about 2 mm. in width, and this was almost totally closed by a cystic protrusion into the cavity from the right lateral wall just above the true cord. The space was somewhat widened with the head flexed.

Lying beneath the epithelium of the medial surface of the right pyriform sinus and intimately a part of the lateral epiglottic wall was the cystic bulge mentioned. It measured 1.6 cm. in diameter and extended from the level of the epiglottic apex downward in the wall, inclining forward slightly and toward the laryngeal cavity, to enter it in the right fossa of Morgagni. In doing this, the bulge pushed the right false cord upward, causing it to arch sharply over the cyst, putting the cord under tension and thinning and flattening it against the laryngeal wall. At this level the cystic mass could be felt but not seen on the outer surface of the larynx. When the cyst was punctured from above, both the para-epiglottic bulge and that protruding into the larynx simultaneously collapsed, with the exudation of about 5 cc. of clear, colorless, odorless serous fluid (fig. 2).

When sectioned transversely, the entire mass was seen to consist of one cyst lined by a dull, pale, smooth surface, which lay in the wall of the epiglottis and larynx, inclining forward and medially as described and covered on the outer surface in its uppermost third by the outer epiglottic lining and throughout the remainder by the laryngeal musculature. It did not communicate with any cavity and showed no solid remnant of tissue extending to its wall from any surface; nor were there any other cysts or solid masses of grossly discernible dimensions in the deeper cervical tissues.

The lungs showed, grossly and histologically, large confluent atelectatic areas interspersed by aerated areas and, along the lower peripheries, by bleblike emphysematous tissue. The remaining thoracic, abdominal and cerebral viscera were not noteworthy grossly.

Microscopically the cyst wall was composed of a dense fibro-elastic, poorly cellular and poorly vascular layer of varying width, which merged into the surrounding laryngeal and epiglottic fibromuscular tissue. It was lined by a single layer of ciliated, columnar epithelial cells, a few of which contained mucoid globules. This lining, studied in serial sections, was nowhere continuous with laryngeal, pharyngeal or epiglottic epithelia, but was separated everywhere from them by the wall of the cyst and the intrinsic fibromuscular tissue of these structures. No other cysts or cell rests were apparent in any other portion of the cervical tissues on histologic examination.

The cyst was of the unilocular branchiogenic type, in the location of the second cleft.

COMMENT

Before delineating the clinical picture, a more detailed résumé of individual signs would not be amiss.

Time of Onset.—The earliest sign—dyspnea—was present at birth in eleven of the cases,[21] in one case [1] on the second day of life and in one case [11] during the third week.

21. Edis,[2] Horne, Porak and Theuvernay,[4] Mix,[5] Stoerck,[7] Chamberlin,[8] Rosenberger,[10] Myerson [12] and our cases 1 and 2.

Summary of Recorded Cases of Cyst of the Larynx in the Newborn

Date of Report	Author	When Noticed	Type of Delivery	Sex	Quality of Respiration	Cyanosis	Cry	Effect of Feeding on Respiration	Physical Findings	Course	Postmortem Observations
1876	Edis	At birth	Normal	Female	Never breathed easily; moaning noise	Not mentioned	Not mentioned	Aggravated the dyspnea	Normal	Patient lived 37½ hours	Cysts size of a large bean, springing from the right side of the larynx
1898	Horne	At birth	Not mentioned	Not mentioned	Noisy; breathed with difficulty	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Cyst ruptured spontaneously at 5 months; breathing relieved	
1902	Porak and Theuvernay	At birth	Not mentioned	Not mentioned	Labored	Persistent	Feeble; spasmodic	Not mentioned	Respiratory sounds prolonged	Patient lived 24 hours	Cyst the size of a cherry in the left laryngo-epiglottic fold, almost occluding the larynx
1907	Mix	At birth	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Patient lived 2 weeks	Asphyxia caused by cyst of epiglottis
1916	Stoerck	At birth	Not mentioned	Female	Stridorous; noisy	When fed	Not mentioned	Aggravated the dyspnea	Prolonged respiration and expiration	Patient lived 5 days	Mucous cyst in the right laryngeal wall
1917	Chamberlin	At birth	Not mentioned	Not mentioned	Inspiratory stridor	Not mentioned	Peculiar; shrill	Not mentioned	Laryngeal examination at 6 months revealed a rounded tumor 2 inches in diameter occupying the right side of the larynx; incision disclosed a brownish, gelatinous material	Uneventful recovery 6 months after operation; no recurrence	
1918	Pünder	At birth	Not mentioned	Female	Stridorous; audible	Not mentioned	Not mentioned	Aggravated the dyspnea	Retraction of supraclavicular and infraclavicular spaces	Lived 1 week	A cystic tumor lying in the right laryngo-epiglottic fold occluding the laryngeal opening
1925	Park and Israel	Second day	Low forceps	Male	Labored; noisy	Present	Not mentioned	Coughed	Tenth week showed patient well nourished; head retracted; lips and finger tips cyanosed; numerous rhonchi over thoracic wall	At tenth week cyst incised and contents evacuated; obstructive signs disappeared	
1927	Rosenberger	At birth	Not mentioned	Not mentioned	Labored	Present	Somewhat hoarse	Not mentioned	Associated with the azygos lobe of the right lung	Lived 1 week	Rounded cystic mass occupying right ventricle; contents clear mucoid material
1932	Our case 1	At birth	Low forceps	Female	Labored	Intermittent	Peculiar; shrill	Took feedings fairly well	Tenth week showed patient fully nourished; head retracted; tongue swollen; funnel-like depression of sternum	Lived 10 weeks	Cystic mass in region of left side of neck; a protrusion of which was found on the anterior epiglottic surface
1932	Our case 2	At birth	Normal	Female	Difficult	Present	Feeble	Too early for feeding	Prolonged expiration and inspiration	Lived 6 hours	Cystic mass in right lateral laryngeal wall just above the vocal cord
1932	Lorie and Lux	Third week	Not mentioned	Male	Labored	Intermittent	Never audible	Regurgitated when fed	At 4½ months, emaciated and deformity of anterior thoracic wall	Tracheotomy and later removal of cyst by radial resection	
1933	Myerson	At birth	Not mentioned	Not mentioned	Stridorous	Transitory	Not mentioned	Difficult	Laryngoscopy revealed reddish translucent mass involving right aryepiglottic fold	Mass incised; mucoid material escaped; stridor returned in 48 hours; lived 20 days	Cystic mass in right pyriform sinus

Respirations.—All of the reports of cases stressed the character of the respirations. These were variously described as labored,[22] stridorous,[23] moaning,[2] noisy moaning [24] and *Krächzen.*[9] In one case stridor was present on inspiration only.

The difficulty in respiration was proportionate to the degree of obstruction produced by the size or the location of the cyst. When the occlusion was almost complete, the breathing was markedly labored and necessitated the use of the accessory muscles of respiration.[25]

Difficulty in breathing was noted to be continuous in nine instances [26] and intermittent in two.[27]

In seven instances [28] it was observed that feeding increased the respiratory difficulty, and that regurgitation and cyanosis resulted. Rosenberger [10] noted in his case that "when nursing, the child seemed relieved of dyspnea." In the remainder of the reports no mention was made of the relationship of the intake of food to respiration.

Relation of Respiration to Position.—Pünder's [9] patient breathed freely only when resting on the right side. When the child was placed on the left side, she turned her head constantly toward the right, until she found a more comfortable position. This was due to the fact that the cyst was situated in the right exterior surface of the epiglottis and by its weight caused the latter to close the laryngeal opening. When the child extended the head, the orifice was widened, permitting the passage of air.

In three of the patients who were observed up to and beyond the tenth week there was marked retraction of the head.[29] When flexion was attempted, respiration became embarrassed or ceased.

Cry.—The cry was described as hoarse, feeble and shrill in three cases.[30] In one case [11] the cry was inaudible, and in another [1] it was described as vigorous.

Cyanosis.—Cyanosis was noted to be transient in one case,[12] persistent in another [4] and present only on crying in a third.[11] No mention of cyanosis was made in the other cases.

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22. Porak and Theuvernay,[4] Mix,[5] Rosenberger,[10] Lorie and Lux [11] and our case 1.

23. Stoerck,[7] Chamberlin,[8] Myerson [12] and our case 2.

24. Park and Israel,[1] Horne,[3] Mix [5] and Stoerck.[7]

25. Porak and Theuvernay,[4] Pünder,[9] Lorie and Lux [11] and our case 1.

26. Park and Israel,[1] Edis,[2] Porak and Theuvernay,[4] Mix,[5] Stoerck,[7] Chamberlin,[8] Pünder [9] and our cases 1 and 2.

27. Rosenberger [10] and Lorie and Lux.[11]

28. Park and Israel,[1] Edis,[2] Stoerck,[7] Pünder,[9] Lorie and Lux,[11] Myerson [12] and our case 1.

29. Park,[1] Lorie and Lux [11] and our case 1.

30. Chamberlin,[8] Rosenberger [10] and our case 1.

Physical Findings.—Physical findings were relatively few. Respiration was sometimes prolonged, and rhonchi or coarse râles were sometimes heard. In three instances [31] no mention of physical changes was made.

A marked retraction of the head was noted on three occasions.[32] In two of the cases [33] there was marked deformity of the thoracic wall with anterior bulging and a lateral depression which were associated with a suprasternal and infrasternal retraction. The percussion note was unaltered in these cases.

In our case 1, because of the prolonged respiratory obstruction, the infant resorted to mouth breathing. In addition, there was a cystic mass the size of a crab-apple which filled the left submaxillary triangle.

Nutrition.—Malnutrition was noted in two cases,[33] and in one case [1] the note "well nourished" was made.

Special Examinations.—In 1917, Chamberlin [8] recorded the first laryngeal examination for cyst of the larynx. He found a large smooth-walled tumor of round, even contour with minute blood vessels on the surface. The mass measured 2 cm. in diameter and occupied the entire right side of the larynx. Incision into the mass resulted in a gush of 1 or 2 drachms of a viscid, almost gelatinous brownish fluid.

In the same year Pünder [9] performed laryngoscopy in his case and found the right vocal cleft pushed medially.

In 1925, Park and Israel [1] by means of direct endoscopy found a cyst the size of a large grape, of a whitish-yellow appearance, with several small blood vessels passing over the anterior surface of the epiglottis. The cyst was incised, and yellowish-white mucus escaped. The remains of the wall of the cyst were cauterized with 10 per cent silver nitrate.

In 1932, Lorie and Lux [11] performed tracheotomy prior to laryngoscopy in their cases. This procedure was deemed necessary because of the infant's extreme condition. When laryngoscopy was resorted to six days later, a large cyst was seen completely occluding the larynx. The wall of the cyst was incised and a mucoid secretion evacuated.

Ten days later examination of the larynx disclosed that the cyst was reforming. Radical resection of the cyst with removal of the upper left half of the larynx and the left half of the epiglottis was resorted to with successful results.

In 1933, Myerson [12] performed direct laryngoscopy on an infant, aged 2 days, revealing a reddish translucent mass involving the right aryepiglottic fold and extending in front of the same side of the epi-

31. Edis,[2] Horne [3] and Mix.[5]

32. Park and Israel,[1] Lorie and Lux [11] and our case 1.

33. Lorie and Lux [11] and our case 1.

glottis. The cyst was incised, and thick glairy mucus escaped. The child died two days later of bronchial pneumonia.

Roentgen examination in one instance [1] revealed no pathologic changes. In case 1 an enlarged mediastinal shadow was noted. In case 8 the roentgen rays showed a collapse of the right lung. (Here the cyst of the larynx was associated with an azygos lobe of the right lung.) The roentgen examination in the case reported by Lorie and Lux [11] gave negative results.

Sex.—In this series of cases two patients [34] were males and five [35] females; in the remaining six cases no mention was made of the sex.

Types of Delivery.—In four cases [36] the delivery was spontaneous. In the case of Park and Israel [1] and in our first case instrumental intervention was resorted to. In the remainder of the series no mention was made of the type.

Course of the Disease.—Nine of the thirteen patients died as a result of obstruction produced by the cyst. Six of the patients died within the first week,[37] one in the second week,[5] one in the third week, and one in the tenth week (case 1).

Four patients survived. Park and Israel [1] obtained a cure in their patient in the tenth week, Lorie and Lux [11] in theirs at 4½ months, and Chamberlin [8] in his at 6 months. Horne's [3] patient was relieved by a spontaneous rupture of the cyst at 5 months.

Clinical Entity of Laryngeal Cyst in the New-Born.—From the cases collected and presented in this paper it is possible to establish a definite clinical entity of cyst of the larynx as a possible cause of asphyxia at birth and in early infancy.

Shortly after birth it is noted that the child's breathing is noisy and somewhat labored, but not feeble, and generally vigorous. The cry has a peculiar feeble, shrill quality. Varying degrees of cyanosis are present. When the head is flexed, respiration becomes difficult, and cyanosis is marked. Relief may be obtained spontaneously by the child or through the action of the attendants in turning the child's head to either side or backward. The direction taken depends on the location and the size of the cyst, the child inclining in such a manner as to throw the cyst away from the laryngeal opening. This finding is of great value in differentiating the condition from other mechanical causes of asphyxia and is therapeutically important, since these cysts, as reported in the literature, are not bilateral. Nursing may be accompanied by coughing and regurgitation.

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34. Park and Israel [1] and Lorie and Lux.[11]

35. Edis,[2] Stoerck,[7] Pünder [9] and our cases 1 and 2.

36. Edis,[2] Porak and Theuvernay,[4] Rosenberger [10] and our case 2.

37. Edis,[2] Porak and Theuvernay,[4] Stoerck,[7] Pünder,[9] Rosenberger [10] and our case 2.

As the cyst gets larger the signs become more intense. The head is retracted backward so as almost to touch the spine. Because of the obstruction higher up, with each inspiratory effort there is a retraction of the sternum which results in a funnel-shaped depression of the lower half of the manubrium, such as is found in the thoracic wall of the cobbler.

Laryngeal examination reveals a mass which partially or completely occludes the larynx.

If the cyst is not interfered with, it may cause death by mechanical asphyxia.

Differential Diagnosis.—Cyst of the larynx must be differentiated from other causes of asphyxia at birth or in early infancy.

In atelectasis, the respiratory efforts are irregular, weak and quiet. The cry is usually absent.

In intracranial hemorrhage a similar picture may be present, but with variations such as a shrill cry, convulsions and a bulging fontanel.

Foreign bodies are ruled out with roentgen and laryngeal examination.

CONCLUSION

Because of its rarity, cyst of the larynx is not kept in mind as a possible cause of asphyxia or dyspnea in childhood and is not looked for. It is our belief that with more extensive use of laryngoscopic and other auxiliary examinations, especially roentgen examination of the neck in two positions (anteroposterior and anterolateral), in cases of afebrile dyspnea in children more cases of so-called idiopathic or paroxysmal dyspnea will be disclosed. Especially do we believe that this is the case when it is recalled how much more frequently such cysts are found in adults than in young persons, and when it is remembered that such cysts are generally congenital pathologically and are only infrequently associated with clinical or pathologic signs of inflammation or neoplasia. When the ease of surgical removal by laryngoscope is taken into consideration, the importance of searching diligently for a cyst becomes manifest.

SUMMARY

1. Two cases of asphyxia due to laryngo-epiglottic cysts in infancy are recorded. The literature is reviewed.

2. A clinical picture of this cause of asphyxia is delineated.

3. This clinical abnormality is differentiated from other more common causes of asphyxia in childhood.

4. The operability and hopeful prognosis are stressed.

Dr. Charles Cassasa, Assistant Medical Examiner, New York City, gave us permission to report case 2.

INFANT FEEDING AND NUTRITION

A DECADE OF PROGRESS

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(*Concluded from page 190*)

MINERAL METABOLISM

In mineral metabolism one has a subject which is capable of more or less exact experimental study and measurement, thus escaping a good deal of the empiricism which has surrounded other phases of infant feeding and nutrition. A comparison of the mineral content of the two chief types of food in the infant's diet, human milk and cow's milk, forms an excellent starting point for the discussion.

Telfer,[145] who has probably done more work than any other single investigator in this field, gave the following analysis of the mineral content in grams per hundred cubic centimeters of human and cow's milk:

	Total Ash	Calcium Oxide	Magnesium Oxide	Phosphorus Pentoxide	Iron
Human milk	0.19	0.043	0.006	0.048	0.0001
Cow's milk	0.73	0.16	0.018	0.21	0.00008

It may be readily seen that in general cow's milk contains approximately four times as much mineral as human milk. The other major difference is the greater absolute and far greater relative iron content of human milk.

It has been pointed out that the mineral content of the diet of a young animal (including man) conforms closely to the requirements for growth. Thus, it is a well known fact that the calf doubles its birth weight in about forty-seven days and the human infant in one hundred and eighty days, so that the rates of growth and the mineral contents of the maternal milks are almost in the same ratio, 4:1. Obviously the human infant, who does not receive the milk of its own species, but receives, instead, cow's milk, is ingesting a food which contains more minerals, save for iron, than it normally should.

However, not only is the actual intake of calcium and phosphorus of importance, but even more so is the question of relative absorption

145. Telfer, S. V.: Mineral Metabolism in Infancy, Glasgow M. J. **113**:246 (May) 1930.

and retention. Telfer [146] conducted carefully measured experiments on 4 infants whose diet was changed from breast milk to cow's milk. The percentage of calcium retention from breast milk ranged from 64 to 90, with an average of 74. The actual amount of calcium oxide retained daily averaged 0.31 Gm. When the infants were fed cow's milk, the percentage of calcium retention ranged from 32 to 59, with an average of 46 per cent. The actual amount retained daily averaged 0.8 Gm. Telfer stated, then, that the actual amount of calcium retained by infants receiving whole cow's milk is from two to three times greater than that retained by infants fed breast milk.

The reports of other investigators have agreed fairly closely with Telfer's. Wang and her associates [147] reported a 61 per cent retention of calcium from breast milk and 46 per cent from cow's milk. The actual daily amounts were 0.45 Gm. for the first group and 0.8 Gm. for the second group. They stated further that the calcium metabolism for breast milk seemed independent of the age of the infant, but with cow's milk, the older the infant, the greater the percentage of retention of minerals. Swanson [148] showed that the retention of all minerals save sulphur was much higher in infants receiving cow's milk. Witt's [149] results are similar, although he investigated the phosphorus retention only. He reported that the percentage of absorption and retention of phosphorus is about the same for the two milks, but, owing to the higher phosphorus content of cow's milk, the absolute amount of mineral retained is higher in the artificially fed infant.

Most of these experiments in mineral metabolism have been conducted for relatively short periods of time, but Boldt and his co-workers,[150] in an effort to determine whether the minerals retained during a period of high mineral intake were actually assimilated and not merely retained for a short time, placed 2 infants on a diet low in minerals (breast milk) for one month, then on a diet high in minerals (cow's milk) for the next month and then back on the first diet for

146. Telfer, S. V.: Mineral Metabolism in Infancy: III. The Substitution of Cow's Milk for Human Milk in Infant Feeding, Glasgow M. J. **114**:265 (Nov.) 1930.

147. Wang, C. C.; Witt, D. B., and Felcher, A. R.: Comparison of Metabolism of Some Mineral Constituents of Cow's Milk and of Breast Milk in Same Infant, Am. J. Dis. Child. **27**:352 (April) 1924.

148. Swanson, W. W.: The Composition of Growth, Am. J. Dis. Child. **43**:10 (Jan.) 1932.

149. Witt, D. B.: Phosphorus Metabolism in Infants, Am. J. Dis. Child. **43**:306 (Feb.) 1932.

150. Boldt, F.; Brahm, C., and Andresen, G.: Langfristige Mineralstoffuntersuchungen an zwei gesunden Säuglingen bei mineralstoffarmer und-reicher Kost, Arch. f. Kinderh. **87**:277 (June) 1929.

a third month. During the third month the excretion of minerals was no higher than it was during the first month, showing that the large amount of minerals retained during the second month was actually assimilated.

It seems to be the consensus, then, that greater amounts of calcium and phosphorus are retained by the infant fed cow's milk because of the greater intake of these minerals. In other words, in breast feeding the mineral intake is low and closely adjusted to requirements for growth; in cow's milk feeding the mineral intake is much greater than the normal requirements, and while the percentage of retention is lower than in breast milk feeding and a large excess is excreted in the stools, the absolute quantities of calcium and phosphorus retained are much higher. One is met, then, with the question: Why is rickets, which is closely related to the amount of calcium and phosphorus retained, more frequent in bottle-fed babies? The question is not easily answered. There are certainly other factors involved besides adequate intake and retention of minerals.

One is not offered much explanatory aid by a comparison of the mineral intake of rachitic and nonrachitic breast-fed infants. Von Meysenbug,[151] in an investigation of the mineral content of the breast milk of mothers with rachitic children and of mothers with normal children, showed that there was no reduction in the inorganic phosphate constituents of the milk in the former group. While he[152] later believed that the calcium content of the milk of mothers with rachitic children was somewhat lower (averaging 27.5 mg. per hundred cubic centimeters) than that of the normal group (averaging 32.6 mg. per hundred cubic centimeters), this was not confirmed by Telfer. The latter found no appreciable differences in the mineral content of maternal milk in rachitic and nonrachitic groups of breast-fed infants.[153]

Other factors, of course, such as the relative amounts of calcium and phosphorus, merit some consideration. In view of earlier conflicting reports, Orr and his associates[154] conducted metabolic experiments on

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151. von Meysenbug, L.: The Inorganic Phosphate Content of Breast Milk of Mothers with Normal and Rachitic Infants, Am. J. Dis. Child. **24**:200 (Sept.) 1922.

152. DeBuys, L. R., and von Meysenbug, L.: The Calcium Content of Breast Milk in Relation to Rickets, Am. J. Dis. Child. **27**:438 (May) 1924.

153. Telfer, S. V.: The Mineral Content of Human Milk in Normal and Rachitic Families, Biochem. J. **18**:809, 1924.

154. Orr, W. J.; Holt, L. E., Jr.; Wilkins, L., and Boone, F. H.: The Relation of Calcium and Phosphorus in the Diet to the Absorption of These Elements from the Intestine, Am. J. Dis. Child. **28**:574 (Nov.) 1924.

2 infants which showed that excessive amounts of calcium in the diet tend to increase the total absorption and retention of calcium but to decrease the retention of phosphorus. Whereas normally the ratio of calcium to phosphorus retention was about 1.3 : 1, with feedings high in calcium, this ratio became 4 : 1 in one case and 12 : 1 in the other. A diet high in phosphorus exerted an unfavorable influence on calcium metabolism, causing a marked decrease in the retention of calcium and a great increase in the calcium content of the stool. Telfer felt that it was difficult to restrict the absorption of phosphorus save by the addition of huge amounts of calcium to a diet poor in phosphorus, and that most commonly any faults lay in insufficient calcium retention.

It has been shown that an infant who is receiving whole milk retains a greater percentage of the total mineral intake than one who is receiving diluted milk. Nelson [155] demonstrated similar findings in nitrogen metabolism. Infants receiving whole milk soon outstripped both average and normal figures for weight and length. This was not merely an accumulation of adipose tissue, for there was also a proportionate increase in the retention of nitrogen. Not only was the total amount of nitrogen retained higher, naturally, but the amount retained represented a greater percentage of the intake than did that of infants receiving ordinary dilutions of milk. The average nitrogen retention of the group receiving whole milk was 27 per cent and of the other group, 19.5 per cent.

The effect of heat treatment of milk on mineral absorption has received some attention under the discussion of evaporated milk. It was shown that the absorption of calcium and phosphorus is probably as good from evaporated milk as from fresh milk. Daniels and Stearns [156] investigated differences in the retention of minerals during the feeding of milk pasteurized for thirty minutes at 145 F. and of milk brought to a quick boil, and found greater retention of minerals from the latter milk. They concluded, therefore, that while pasteurization may be the best method of safeguarding the milk, it does not seem to be the most satisfactory from the standpoint of fulfilling the physiologic needs of the infant. Budde,[157] however, found that boiling distinctly diminished the amount of ultrafiltrable calcium, but that pasteurization effected little change.

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155. Nelson, M. V. K.: The Growth and Nitrogen Metabolism of Infants Receiving Undiluted Milk, Am. J. Dis. Child. **39**:701 (April) 1930.

156. Daniels, A. L., and Stearns, G.: The Effect of Heat Treatment of Milk Feedings on the Mineral Metabolism of Infants, J. Biol. Chem. **61**:225 (Aug.) 1924.

157. Budde, O.: Untersuchungen zur Verdauungsphysiologie des Säuglings: über den Lösungszustand von Kalk und Phosphat im Chymus, Ztschr. f. Kinderh. **50**:482, 1930.

A great deal of attention has been paid to the effect of acid milk feeding and the acidity of the gastric contents on the retention of minerals. Telfer [158] showed that the absorption of calcium is dependent on an acid medium, and must therefore be limited to a small portion of the upper part of the intestine, as the greater part of the intestinal tract has an alkaline reaction which causes precipitation of the calcium in the form of insoluble phosphates. It has been demonstrated that a high alkalinity of ingested food can cause a defective absorption of calcium, and the fact that cow's milk contains a considerably greater amount of buffer substances than breast milk and is consequently much more potentially alkaline explains why the relative retention of minerals is less from cow's milk. It has been shown that the amount of calcium dialyzed out of cow's milk reaches its peak only after the addition of 50 per cent by volume of decinormal hydrochloric acid, while only 15 per cent by volume of acid need be added to breast milk to insure the maximum dialysis of calcium.[159]

That calcium absorption is dependent on the hydrogen ion concentration of the upper part of the intestinal tract seems to be definitely proved. Not only is the acid reaction necessary for the conversion of insoluble calcium phosphates to soluble calcium chloride, but the absorption of calcium chloride itself is dependent on the hydrogen ion concentration, as Irving and Ferguson [160] demonstrated. They injected into the intestines a solution of calcium chloride buffered at various levels of p_H value and noted the amount of absorption of calcium by determining the blood calcium. It was shown definitely that a higher absorption took place from an acid than from a neutral or alkaline solution.

Acid milk feedings insure an acid medium and solubility of the calcium salts. That this type of feeding raises the retention of minerals and hence offers some protection against rickets seems indubitable. Flood [161] showed that hydrochloric acid milk increases the retention of calcium in rachitic infants although it had no such effect in normal children; the more severe the rickets, the greater were the results obtained by the acid milk. It is easy to analyze the reason for this: Both rachitic and tetanic infants show a moderate hypochlorhydria, and

158. Telfer, S. V.: Studies in Calcium and Phosphorus Metabolism and Absorption of Calcium and Phosphorus and Their Fixation in Skeleton, Quart. J. Med. **17**:245 (April) 1924.

159. Zotterman, Y.: Studies in Calcium Dialysis from Cow's Milk and Human Milk, Acta pædiat. **5**:180, 1925.

160. Irving, L., and Ferguson, J.: The Influence of Acidity in the Intestine upon the Absorption of Calcium Salts by the Blood, Proc. Soc. Exper. Biol. & Med. **22**:527, 1925.

161. Flood, R. G.: Calcium Balance with Hydrochloric Acid Milk, Am. J. Dis. Child. **32**:550 (Oct.) 1926.

consequently have difficulty in both saturating the buffers present in cow's milk and providing a sufficiently acid medium to convert the calcium into soluble calcium chloride. Experimental work in animals has confirmed this. Jones [162] was able to produce rickets in puppies by increasing the alkalinity of the food through the addition of an alkaline salt and to cure the condition by the addition of hydrochloric acid to the diet. Abrahamson and Miller [163] showed that the gastro-intestinal tract of rats given a rachitic diet had a decreased acidity. The addition of cod liver oil to the diet definitely lowered the p_H to the acid side with consequent improvement of the retention of minerals and the rickets. Scheer [164] has also cured tetany by the use of hydrochloric acid milk. Inouye's [165] work is also of interest. He demonstrated that the enteral administration of lactose or galactose served to prevent the onset of tetany in parathyroidectomized dogs almost indefinitely, while severe tetany developed within a few days if other carbohydrates were used. That the action of lactose is local was proved by the fact that parenteral administration was ineffective. Inouye felt that lactose stimulates the production of flora in the intestine which produce acid with a consequent increase in the absorption of calcium.

An occasional note of contention has arisen. Wills and her associates [166] found that in some infants the retention of calcium was decreased following the feeding of hydrochloric acid milk in spite of increased gastric acidity. They believed that in healing rickets the increase in gastric acidity which usually occurs runs parallel, not with the increased retention of calcium, but with the general condition of the child. Thoenes [167] investigated the mineral content of the bones of dogs which were fed acid milk. In only 1 case was there an increase in the mineral content as compared with dogs that were fed sweet milk. However, I believe that one is safe in saying that acid milk feeding

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162. Jones, M. R.: Hydrochloric Acid Therapy in Rickets, J. A. M. A. **82**:439 (Feb. 9) 1924.

163. Abrahamson, E. M., and Miller, E. G.: Hydrogen Ion Concentration in the Gastro-Intestinal Tract of the Albino Rat, Proc. Soc. Exper. Biol. & Med. **22**: 438, 1925.

164. Scheer, K., and Salomon, A.: Hydrochloric Acid Milk in Tetany, Monatschr. f. Kinderh. **27**:406 (Jan.) 1924.

165. Inouye, T.: Experimental Tetany and Diet, Am. J. Physiol. **70**:524 (Nov.) 1924.

166. Wills, L.; Sanderson, P., and Paterson, D.: Calcium Absorption in Relation to Gastric Acidity: Study of Rickets, Arch. Dis. Childhood **1**:245 (Aug.) 1926.

167. Thoenes, F.: Ueber den Einfluss saurer Milchmischungen auf die chemische Zusammensetzung des wachsenden Hundeorganismus, Monatschr. f. Kinderh. **36**:208, 1927.

insures the conversion of the insoluble calcium phosphate to soluble calcium chloride and raises the retention of calcium, probably more markedly in rachitic infants who exhibit hypochlorhydria than in normal infants.

Of the other minerals in milk, iron is probably the only one which, at present, is of interest to the pediatrician. Telfer stressed the relatively minute quantity of iron in cow's milk and showed that the relative retention of even the small amount present is much lower than in breast milk. The reports on the iron content of breast milk vary somewhat. Hill [168] reported 0.55 mg., and Telfer, 1 mg. per liter. Dorlencourt and his associates [169] found on analysis that the iron content of breast milk varied from 1.4 to 7 mg. per liter, with a general average of 3 mg. The age of the lactating mother exerted some influence: the milk of young mothers averaged 2 mg. per liter, increasing to a maximum of 4 mg. at the age of 27 and decreasing to 2.5 mg. in the fourth decade. Parity had little effect on the iron content of the milk. Definite increases in the iron content of the milk were obtained by giving iron salts by mouth, and it was felt that lactating mothers of anemic children should receive iron therapy. As to the iron requirements of the child, Telfer stated that a baby weighing 7 Kg. needs about 1 mg. of iron a day; Hill thought that an infant 1 year old requires about 2 mg. a day, and Leichseuring and Flor [170] place the requirement at about 8 mg. a day for a child of 3 or 4 years. Hill expressed the opinion that the average full-term baby has sufficient iron stored up to make up for any deficiency in its diet up to about the eighth month of life. Therefore additional food given at that time should contain as much iron as possible. He compared the iron content of a few foods with that of milk: human milk, 0.55 mg. per liter; cow's milk, 0.17 mg. per liter; egg yolk, 1.4 mg. per yolk; spinach, 0.59 mg. per tablespoonful, and prune sauce, 0.7 mg. per tablespoonful. Following a study of London children, MacKay [171] observed that anemia is common in infants and that artificially fed babies begin to show evidences of it as early as the third month of life. She felt that iron should be administered as a routine, just like cod liver oil or orange juice.

168. Hill, L. W.: Pigment and Iron in Infants' Diet: Their Relation to Hemoglobin Formation, Boston M. & S. J. **191**:342 (Aug. 21) 1924; Iron in Infant's Diet, M. Clin. North America **8**:1591 (March) 1925.

169. Dorlencourt, H., and Calugareancu-Nandris: Le fer dans le lait de femme, son dosage, ses variations, Nourrisson **17**:227 (July) 1929.

170. Leichseuring, J. M., and Flor, I. H.: The Iron Requirement of the Preschool Child, J. Nutrition **5**:141 (March) 1932.

171. MacKay, H. M. M.: Nutritional Anemia in Infancy, Proc. Roy. Soc. Med. **22**:38 (Nov.) 1928.

VITAMINS

There remains, finally, the problem of vitamins. The importance of vitamins in the human dietary has been known to a certain extent for many years, but needless to say the emphasis placed on the rôle of vitamins in the modern infant dietary has been tremendous. To review the whole subject would require a book in itself, so limitation must be made to a few important conclusions on the comparative vitamin content of human and cow's milk and the problem of increasing the vitamin D content of cow's milk.

Macy and Outhouse [172] wrote a fairly comprehensive review of some phases of this subject. In their experimental studies of vitamin A, rats were depleted of their reserve of vitamin A, a condition heralded by cessation of growth, infections of the respiratory tract and xerophthalmia. From 2.5 to 3 cc. of either human or cow's milk was sufficient to cure animals of xerophthalmia and allow for growth. Even less was required for preventive purposes. Thus, both breast and cow's milk are relatively good sources of vitamin A. They emphasized the fact that in the United States one is rarely confronted with a gross deficiency of vitamin A appearing as xerophthalmia, but rather with such borderline conditions as anorexia, cessation of growth and susceptibility to infections of the respiratory tract. Daniels,[173] in fact, felt that the high incidence of infection of the upper respiratory tract in bottle-fed babies might be related to a relative deficiency of vitamin A due to relatively poorer absorption of that factor by infants receiving cow's milk. To test this theory she fed ether extracts of stools of breast-fed and artificially fed infants to rats in which signs of a deficiency of vitamin A had developed. The rats which received extracts of the stools from breast-fed infants failed to improve, while the other group showed definite improvement in symptoms, showing that some vitamin A had passed through unabsorbed in the stools of infants receiving cow's milk. Macy and Outhouse pointed out that the nursing mother should have an abundance of vitamin A, as it appears in her milk only if present in her food, the body being incapable of synthesizing it. They further stressed the fact that while cow's milk contains about the same amount of vitamin A as breast milk originally, it may lose a good deal of it through the various processes it may undergo. Thus, the vitamin readily undergoes deterioration, through oxidation, by drying, repeated heating or heating at high temperatures in the presence of air and by aging. Skimmed milk, too, is deficient in this vitamin, as the greater part of

172. Macy, I. G., and Outhouse, J.: The Vitamin Content of Milk Used in Infant Feeding, Am. J. Dis. Child. **37**:379 (Feb.) 1929.

173. Daniels, A. L.: Vitamin A Content of Fetal Excretion of a Breast Fed and Artificially Fed Infant, Proc. Soc. Exper. Biol. & Med. **23**:824, 1926.

it is found in the fat moiety of the milk. They issued the warning, then, that part of the vitamin A content may be destroyed in the manufacture of various prepared milks. They believed that adjuvants rich in vitamin A should be added to the diet of both breast-fed and artificially fed babies.

Both breast milk and cow's milk are relatively poor in vitamin B content. The latter is somewhat superior, judging from experiments on animals. The vitamin B content of milk is only about one tenth to one fifteenth of the vitamin A content. It has been shown, too, that vitamin B cannot be stored for a number of weeks as can vitamin A, for growth in rats ceases quickly on diets deficient in vitamin B. If human milk is added to these diets, fair growth is maintained on the daily addition of 16, 18 or 20 cc. Sexual maturity is postponed with amounts less than 18 cc., and a normal estrus cycle necessitates the addition of 20 cc. If, similarly, cow's milk is added to the deficient diets, fair growth is achieved on from 12 to 16 cc. Growth was better on the addition of 20 cc. of cow's milk than with from 30 to 35 cc. of human milk. In experiments with the separate components of vitamin B—B_1 and B_2, or the thermolabile and thermostabile elements—it appeared that cow's milk contained more of the pellagra-preventive factor than of the antineuritic element, while the reverse was true of human milk. Hunt and Krauss [174] agreed that cow's milk is relatively poor in the antineuritic factor and relatively potent in the B_2 or G factor.

Hoobler [175] emphasized the symptoms of deficiency of vitamin B in infants. While beriberi as it exists in the Philippine Islands and in the Orient is not often seen in the United States, he believed that occasionally a complex of symptoms is seen consisting of anorexia, loss of weight, spasticity of the extremities, rigidity of the neck, restlessness and fretfulness, pallor and a low hemoglobin content which is helped by the administration of vitamin B. Dennett [176] expressed the opinion that vitamin B should be added to the infant's diet as a routine, as are vitamins C and D. Others [177] have also stressed the fact that the vitamin requirements, especially vitamin B, of malnourished infants are especially high, and that sick infants are frequently given weak formulas

174. Hunt, C. H., and Krauss, W. E.: The Relative Antineuritic and Antipellagric Potency of Milk, J. Biol. Chem. **79**:733 (Oct.) 1928.

175. Hoobler, B. R.: Symptomatology of Vitamin B Deficiency in Infants, J. A. M. A. **91**:307 (Aug. 4) 1928; Use of Vitamin B in Diets of Infants, ibid. **96**:675 (Feb. 28) 1931.

176. Dennett, R. H.: Routine Use of the Vitamin B Factor in Infant Feeding, J. A. M. A. **92**:769 (March 9) 1929.

177. Frölich, T.: Vitamin Requirements of Malnourished Infants, Acta pædiat. **4**:247, 1924.

so long that deficiency diseases develop. Gunderson and Steenbock [178] showed that increasing the vitamin B intake of cows had little effect on the vitamin B content of the milk. They felt that the maximum vitamin B content of milk is under definite physiologic control.

Little that is new has been added to the knowledge of the antiscorbutic factor. However, it has been definitely established that breast milk as well as cow's milk may be deficient in vitamin C. A sufficient number of cases of scurvy in breast-fed infants have been reported to lead one to supply additional vitamin C to breast-fed babies as well as to infants artificially fed, as part of the routine. Hughes,[179] upsetting previous reports, showed also that little if any additional vitamin C can be supplied to cow's milk by increasing the ingestion of that factor by the animals.

As for vitamin D, volumes have been written about it in the past decade. Products have been fortified in vitamin D until the super-super stage has now been reached. One must, perforce, limit this discussion to a consideration of the vitamin D content of cow's milk and a brief perusal of the methods proposed for augmenting that content. Cow's milk contains relatively more vitamin D than does breast milk. As Macy and Outhouse demonstrated, results of experiments in animals testing the vitamin D content of milk and other substances have been confusing, because in rats the calcium-phosphorus ratio must first be adjusted. Following this adjustment it was shown that 40 cc. of breast milk was ineffective in curing rats with rickets while 30 cc. of cow's milk caused considerable healing. Hess and Weinstock [180] also showed that human milk is poor in antirachitic factors. They also pointed out that susceptibility to rickets, unlike scurvy, is in direct ratio to the consumption of milk. That is to say, a child who receives a quart of milk a day is less apt to have scurvy develop than one who ingests only a pint of milk a day, but the reverse is true of rickets. It is evident, then, that from a nutritional standpoint there is an essential etiologic difference between rickets and the other disturbances. It was demonstrated previously that an adequate mineral diet also does not insure against the development of rickets.

Attempts to increase the vitamin D content of breast milk have already been discussed. Naturally, even more intensive efforts have

178. Gunderson, F. L., and Steenbock, H.: Is the Vitamin B Content of Milk under Physiological Control? J. Nutrition **5**:199 (March) 1932.

179. Hughes, J. S.; Fitch, J. B.; Cave, H. W., and Riddell, W. H.: Relation Between the Vitamin C Content of a Cow's Ration and the Vitamin C Content of Its Milk, J. Biol. Chem. **71**:309 (Jan.) 1927.

180. Hess, A. F., and Weinstock, M.: A Study of the Antirachitic Factor in Human and in Cow's Milk, Am. J. Dis. Child. **34**:845 (Nov.) 1927.

been made toward raising the vitamin D content of cow's milk. These efforts have been directed in two main channels: (1) irradiation of the milk, and (2) feeding of vitamin D concentrates to cows. Milk already fortified in vitamin D is naturally of advantage in that it provides an automatic form of therapy, no longer necessitating the addition of cod liver oil to the infant's dietary.

The efficacy of irradiation of milk as a means of increasing its vitamin D content has been definitely proved. Hess [181] and Steenbock,[182] in 1924, were the first to demonstrate that antirachitic properties could be imparted to inert fluids by means of irradiation by carbon arc or mercury vapor arc lamps. Since then a great deal of work has been done in a comparatively short time. Supplee [183] has been active in this field. He showed that both the carbon arc lamp and the quartz mercury vapor arc lamp are capable of producing about the same concentration of vitamin D when comparable amounts of energy are used. Kramer [184] soon demonstrated, clinically, the efficacy of this milk in the healing of rickets. He showed that the retention of minerals was increased in rachitic infants and the serum phosphorus content raised. Daniels and her co-workers [185] also found that the ingestion of irradiated milk increased the retention of minerals. Hess [186] showed that irradiation for sixteen seconds makes milk highly antirachitic, so that less than a quart a day protects even colored children. Essig [187] demonstrated that skimmed irradiated milk is not effective, proving that the vitamin is intimately bound up with the fat content of the milk. It was felt, at first, that irradiation destroyed some of the vitamin A present, but later

181. Hess, A. F., and Weinstock, M.: Antirachitic Properties Imparted to Inert Fluids by Ultraviolet Irradiation, J. A. M. A. **83**:1558 (Nov. 15) 1924.

182. Steenbock, H., and Black, A.: Fat-Soluble Vitamins: Induction of Growth-Promoting and Calcifying Properties in Ration by Exposure to Ultra-Violet Light, J. Biol. Chem. **61**:405 (Sept.) 1924.

183. Supplee, G. C.; Dorcas, M. J., and Hess, A. F.: Irradiated Milk: the Energy Requirements for Antirachitic Activation, J. Biol. Chem. **94**:749 (Jan.) 1932. Supplee, G. C.; Hanford, Z. M.; Dorcas, M. J., and Beck, H. H.: Irradiated Milk: the Amount of Vitamin D and Its Rate of Formation, ibid. **95**:687 (March) 1932. Supplee, G. C.: Antirachitic Activation of Milk by Direct Irradiation with Ultra-Violet Rays, Am. J. Pub. Health **23**:225 (March) 1933.

184. Kramer, B.: Rickets in Infants: Treatment with Irradiated Milk, Am. J. Dis. Child. **30**:194 (Aug.) 1925.

185. Daniels, A. L.; Stearns, G., and Hutton, M. K.: Calcium and Phosphorus Metabolism in Artificially Fed Infants: I. Influence of Cod Liver Oil and Irradiated Milk, Am. J. Dis. Child. **37**:296 (Feb.) 1929.

186. Hess, A. F., and Lewis, J. M.: Milk Irradiated by the Carbon Arc Lamp, J. A. M. A. **99**:647 (Aug. 20) 1932.

187. Essig, B.: Rachitis-Prophylaxe durch bestrahlte Milch, München. med. Wchnschr. **78**:273 (Feb. 13) 1931.

workers [188] agreed that if too long an exposure is avoided there is no destruction of vitamin A. Supplee and Dow [189] showed experimentally that irradiation caused a slight but measurable decrease in the vitamin C content. Irradiation of dried milk caused no evident destruction of the antiscorbutic elements. In a study of the antirachitic value of irradiated powdered milk, DeSanctis and his associates [190] fed this reliquefied product to 30 infants, of whom 24 were fully protected, 5 were protected clinically but showed positive roentgen findings of rickets, and 1 child was not protected at all. When only 25 per cent irradiated milk was used, rickets developed in 50 per cent of the subjects. Scheer [191] felt that sometimes the taste and smell are affected, owing to oxidation in exposure of the milk to ultraviolet rays. He overcame this by passing carbon dioxide through the milk or by irradiating it in an atmosphere of carbonic acid gas.

Steenbock [192] was the first to show that the ingestion of irradiated yeast by cows increased the antirachitic potency of their milk. As Krauss [193] pointed out, the more natural method of increasing the vitamin D content of milk would be to feed the cows irradiated yeast, viosterol or some other concentrate of vitamin D, as this eliminates further handling of the milk. However, it would be difficult to follow closely, because of the long experimental work involved, the potency of a milk supply the vitamin D content of which was dependent on the feeding operations carried on over scattered areas, so that at present the feeding method is practical only for special and carefully supervised herds. Krauss showed that the vitamin D content of the butter-fat of the milk was increased from 0.17 Steenbock rat unit per gram to 2.5

188. Supplee, G. C., and Dow, O. D.: Vitamin A Potency of Irradiated Milk, J. Biol. Chem. **75**:227 (Oct.) 1927. Bender, R. C., and Supplee, G. C.: Vitamin A Content of Milk Irradiated by Various Carbon Arcs, Am. J. Dis. Child. **45**:995 (May) 1933. Nabarro, D., and Hickman, J. O.: The Irradiation of Milk for the Increasing of Its Antirachitic Potency, Lancet **1**:127 (Jan. 18) 1930.

189. Supplee, G. C., and Dow, O. D.: The Effect of Ultraviolet Radiation on the Antiscorbutic Vitamin of Liquid and of Dry Milk, Am. J. Dis. Child. **41**:1353 (June) 1931.

190. DeSanctis, A. G.; Ashton, L. O., and Stringfield, O. L.: A Study of the Antirachitic Value of Irradiated Powdered Whole Milk, Arch. Pediat. **46**:297 (May) 1929.

191. Scheer, K.: Die Behandlung der Rachitis mit in Kohlensaüreatmosphäre bestrahlter Milch, München. med. Wchnschr. **75**:642 (April 13) 1928.

192. Steenbock, H.; Hart, E. B., and Hanning, F.: Fat-Soluble Vitamins: XXX. The Antirachitic Value of Cow's Milk as Modified by the Feeding of Irradiated Yeast, J. Biol. Chem. **88**:197 (Aug.) 1930 .

193. Kraus, W. E.; Bethke, R. M., and Monroe, C. F.: The Effect of Feeding Irradiated Ergosterol to Cows on the Vitamin D Content of Milk, J. Nutrition **5**:467 (Sept.) 1932.

units per gram when 200,000 rat units of viosterol were fed each day to the cows. Gerstenberger's [194] experience with this milk seemed disappointing, however, from a curative standpoint. Two rachitic infants received, daily, 1 pint of "yeast" milk plus 1 pint of skimmed milk and sufficient carbohydrate to meet their caloric needs. It was shown that the milk possessed antirachitic powers, but they were not of great magnitude. The bones of the 2 infants were not completely healed at the end of ten and eleven weeks, respectively. The blood calcium levels became normal only after the tenth week, and the phosphorus levels had not attained a normal value by the end of the experiment. It was estimated on the basis of practical experience with cod liver oil that a pint of milk contained slightly less than a half teaspoonful of cod liver oil.

Others' experience with vitamin D milk has been more favorable. Hess [195] fed from 30,000 to 60,000 rat units of irradiated yeast and from 100,000 to 200,000 units of viosterol to cows, and fed the milk produced to four groups of infants. The milk from the former group seemed more potent, considering the number of units administered, but both milks were effective. Wyman and Butler [196] fed "yeast" milk to 2 infants and 2 older children with rickets and produced definite healing and an increase in the serum calcium and phosphorus. A later report of Wyman [197] was also favorable. Kramer and Gittleman [198] tested both types of vitamin D milk in a group of rachitic infants, and found them equally effective as curative agents, even when the milk supplied only 40 units a day to the infants. Kramer, as Hess did previously, put this question: Why is the minimal effective dose of vitamin D in the form of vitamin D milk so much smaller than in the form of cod liver oil or viosterol? Watson [199] had previously discussed this question without arriving at a satisfactory answer in his paper on the "vital" factor in diet. He, too, stressed the fact that according to biologic tests the increase in the amount of antirachitic substance in milk effected by

194. Gerstenberger, H. J., and Horesh, A. J.: The Treatment of Rachitic Infants with Milk Produced by Cows Fed Irradiated Ergosterol, J. Nutrition **5**:479 (Sept.) 1932.

195. Hess, A. F.; Lewis, J. M.; MacLeod, F. L., and Thomas, B. H.: Antirachitic Potency of the Milk of Cows Fed Irradiated Yeast or Ergosterol, J. A. M. A. **97**:370 (Aug. 8) 1931.

196. Wyman, E. T., and Butler, A. M.: Antirachitic Value of Milk from Cows Fed Irradiated Yeast, Am. J. Dis. Child. **43**:1509 (June) 1932.

197. Wyman, E. T.: Vitamin D Milk, New England J. Med. **209**:889 (Nov. 2) 1933.

198. Kramer, B., and Gittleman, I. F.: Vitamin D Milk in the Treatment of Infantile Rickets, New England J. Med. **209**:906 (Nov. 2) 1933.

199. Watson, C.: The "Vital" Factor in Diet: A Theory of the Nature of Vitamins, Tr. Med.-Chir. Soc. Edinburgh **45**:91, 1931.

irradiation (or by the feeding of vitamin D concentrates) is, from the laboratory standpoint, trifling in comparison with the relatively large amounts of vitamin D present in various medicinal substances such as viosterol. Yet vitamin D milk has been known to cure patients with rickets who failed to respond to the other preparations. He offered several tentative explanations: Is it possible that the commercial preparations lost their curative powers, while milk has the advantage of being consumed in the fresh state?[200] Or has vitamin D milk some property of value which is not determinable by present laboratory tests for vitamin D? These queries only serve to emphasize how little is actually known about vital processes in general and rickets and vitamin D in particular.

200. Dried irradiated milk, however, seems to be effective even after long periods.

FOOTNOTES OMITTED FROM PREVIOUS INSTALMENT

143. Lewis, M. S.: A Comparative Study of Certified and Pasteurized Milk in Infant Feeding, Arch. Pediat. **46**:85 (Feb.) 1929.

144. Ladd, M.; Evarts, H. W., and Franks, L. W.: The Relative Efficiency of Certified and Pasteurized Milk in Infant Feeding, Arch. Pediat. **43**:380 (June) 1926.

Pediatric Biographies

JAMES PARKINSON
1755–1824

A NOTE ON THE HISTORY OF APPENDICITIS IN CHILDREN

JOHN RUHRÄH, M.D.
BALTIMORE

James Parkinson, according to the parish register of St. Leonard's, Shoreditch, London, was born on April 11, 1755. The family lived in Hoxton Square, in the East Center of London, and were evidently well-to-do, the father, John Parkinson, being a surgeon. Little is known of Parkinson's life, but he attended a course of John Hunter's lectures on surgery in 1785, and as his father died in 1784 it is likely that he entered practice at that time. L. G. Rowntree [1] managed to collect considerable information about Parkinson by delving through his books. One of them, called "The Hospital Pupil," was written in 1800 for the parents of those who were destined to study medicine or surgery. In this book Parkinson spoke in the highest terms of the value of an apprenticeship in a hospital, and it is fair to conclude that he was writing from his own experience.

When 26 he married, and his second son studied medicine, became a member of the Royal College of Physicians and carried on the practice at No. 1, Hoxton Square. Parkinson was a radical and a reformer, and he lived through the period of the war for independence of the American colonies and of the French Revolution. He was a member of a number of secret organizations, and in 1794 he wrote "Revolution Without Bloodshed; or Reformation Preferable to Revolt," which title has a familiar sound in these days. One of his connections was with the London Corresponding Society. Several members of this organization were arrested and charged with complicity in what is known as the "Pop-gun plot," which was a plan to murder George III by shooting him during a play with an arrow discharged from a pop-gun. Parkinson was not among those arrested, but he came to their defense and wrote, "A Vindication of the London Corresponding Society" in which

1. Rowntree, L. G.: Bull. Johns Hopkins Hosp. **23**:32, 1912.

he maintained the innocence of those imprisoned. He wanted the Habeas Corpus Act suspended and the prisoners freed. He also was interested in collecting money for the members of the families of those imprisoned. He wrote a long letter to one of the accused in which he outlined his part in their defense and gave the details of his examination by Pitt when he appeared before the Privy Council. Any one reading the transcript of this must be struck by the fact that Parkinson was a very brave man.

In spite of his many duties and interests, he found time for studies in geology and particularly in paleontology and for the study of organic fossil remains, and he was one of the original members of the London Geographical Society. He was an enthusiastic collector and wrote a book in three volumes, "Organic Remains of a Former World," which appeared in 1804, 1808 and 1811. In 1822 he published his "Outlines of Orcytology," which was an introduction to the study of organic fossils. Many of his illustrations were afterward used by Mantell in his "Pictorial Atlas of Organic Remains," in which he paid high tribute to Parkinson as a pioneer in the field. Parkinson was also interested in chemistry and wrote a little book, "The Chemical Pocketbook; or Memoranda Chemica," which went through several editions, at least two of which were printed in the United States.

Another book written by Parkinson is a tale for children, entitled "Dangerous Sports," which appeared in 1800 and again in 1808, and is a forerunner of the safety education now much in vogue. He wrote on improving trusses, on "mad houses" and on gout and two books on medicine intended for the laity, one of which, "The Villager's Friend and Physician" (1800), contains "cursory observations on the treatment of children." "Observations on the Excessive Indulgence of Children" appeared in 1807.

Parkinson's chief contribution was his "Essay on Shaking Palsy," which condition bears his name although it is often called paralysis agitans. This appeared in 1817 and contains the histories of six cases and a most excellent description, which should be read. Unfortunately it is too long to quote here. Parkinson's definition of the disease is: "involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace; the senses and intellect being uninjured." In 1812 he read a paper on "A Case of Diseased Appendix Vermiformis," which was printed subsequently in the *Transactions Medico-Chirurgical*.[2] This is one of the

2. Parkinson, James: Med.-Chir. Tr., London **3**:57, 1816.

early references to the disease in the English medical literature and is reprinted here as a good example of an early report of a case of ruptured appendix in a child.

CASE

OF

DISEASED APPENDIX VERMIFORMIS

BY JOHN PARKINSON, ESQ. SURGEON

COMMUNICATED

BY JAMES PARKINSON, ESQ.

Read January 21, 1812

A PREPARATION of diseased appendix vermiformis in my possession, was removed from a boy about five years of age, who died under the following circumstances.

He had been observed for some time to decline in health, but made no particular complaint until two days before his death, when he was suddenly seized with vomiting, and great prostration of strength. The abdomen became very tumid and painful upon being pressed: his countenance pale and sunken, and his pulse hardly perceptible. Death, preceded by extreme restlessness and delirium, took place within twenty-four hours.

Upon examination, the whole surface of the peritoneum was found inflamed, and covered with a thin coat of coagulable lymph; and slight adhesion had taken place between the peritoneum covering the viscera, and the parietes of the abdomen. The viscera, independent of the inflammation of their peritoneal covering, appeared in a perfectly healthy state, excepting the appendix vermiformis of the coecum. No diseased appearance was seen in this part near to the coecum; but about an inch of its extremity was considerably enlarged and thickened, its internal surface ulcerated, and an opening from ulceration, which would have admitted a crow-quill, was found at the commencement of the diseased part, about the middle of the appendix, through which it appeared that a thin, dark-coloured, and highly fetid fluid, had escaped into the cavity of the abdomen.

Upon opening the appendix, a piece of hardened foeces was found impacted in that part of it which lay between the opening, and that portion of the appendix, which was not evidently marked by disease.

Pediatrics in Art

CRETIN OR MONGOL, OR BOTH TOGETHER

JOHN RUHRÄH, M.D.
BALTIMORE

A painting of extraordinary pediatric interest hangs in the Boston Museum of Fine Arts, a Madonna and Child by Andrea Mantegna (1431-1506), who helped link the mystical middle ages with the mate-

Cretin, mongol or a combination of the two.
(Courtesy of Dr. Harold L. Higgins of Boston.)

rialism which was to follow. Mantegna, favorite pupil of Squarcione, who adopted him and made him his heir, created a new style, and credit is due him for some of the most beautiful paintings in existence.

The child in the picture presents a diagnostic puzzle, for he shows some features of a cretin and some of a mongol and perhaps a mixture

of the two, a clinical picture occasionally seen. Against the diagnosis of cretinism is the lack of tissue changes about the eyes, but the hair is coarse, the tongue is prominent, the mucous membranes are thick and the hands are square, and there are an edematous appearance of the tissues and a suggestion of a fat pad in the neck. Suggestive of mongolism are the slant eyes, although the epicanthic fold is not definite, the small nose, the open mouth and the adenoidal expression; in fact, this is a good example of the appearance caused by obstructed nasal breathing, even though it remained for Meyer to note it in 1869. There is also a suggestion of a curved little finger, and the feet have the great toe separated from the others. The mother has a small goiter. Dr. Harold L. Higgins of Boston called my attention to this picture, and his comments on it are used in this presentation.

News and Comment

GENERAL

American Board of Pediatrics.—The following men have been certified since the last report by the American Board of Pediatrics, on January 16: Sterling Hindley Ashmun, Dayton, Ohio; Walter C. Bacon, Baltimore; Henry Lambert Bibby, Kingston, N. Y.; Guy L. Bliss, Long Beach, Calif.; Thomas Ellwood Buckman, Jacksonville, Fla.; Craig D. Butler, Oak Park, Ill.; Harvey F. Garrison, Jackson, Miss.; John King Glen, Houston, Texas; David Greer, Houston, Texas; Hyman Green, Boston; Paul M. Hamilton, Alhambra, Calif.; Oliver W. Hill, Knoxville, Tenn.; Hughes Kennedy Jr., Birmingham, Ala.; Jacob Carl Krafft, Chicago; James G. Kramer, Akron, Ohio; Frank H. Lancaster, Houston, Texas; Abraham Levinson, Chicago; Edgar W. Loomis, Dallas, Texas; T. D. McCrummen, Austin, Texas; Henry S. Meyer, Houston, Texas; Frederick Bingham Miner, Flint, Mich.; James H. Park Jr., Houston, Texas; J. Buren Sidbury, Wilmington, N. C.; R. E. Ramsay, Pasadena, Calif.; Lewis K. Sweet, San Antonio, Texas; William M. Taylor, Oklahoma City; T. A. Tumbleson, Beaumont, Texas; Damon Walthall, Kansas City, Mo.; Antonio J. Waring, Savannah, Ga.; C. H. Webb, Shreveport, La.; Carl Edward Weigele, Jersey City, N. J.; Noel C. Womack, Jackson, Miss., and Edward J. Wynkoop, Syracuse, N. Y.

Eight of the men in this group were examined. At that examination eleven applicants were examined; eight passed and three failed. In group 1 two passed and none failed; in group 2 two passed and one failed; in group 3 four passed and two failed.

Postgraduate Course in Pediatrics.—The pediatricians of Louisville, Ky., under the auspices of the American Academy of Pediatrics, will give a practical postgraduate course in pediatrics each Wednesday, beginning April 24 and extending to July 1. The lecturers will utilize the patients in the Children's Free Hospital, where the course will be held. The hours will be from 9 to 12 a. m. and from 12:30 to 1:30 p. m., which will enable physicians living within from 75 to 100 miles of Louisville to put in intensive work and get back home in time to take care of any necessary calls. The charge for the course will be $5. Correspondence should be directed to Dr. Philip F. Barbour, state chairman of the American Academy of Pediatrics.

The Children's Free Hospital also extends an invitation to any physician visiting Louisville to spend a day or week in the wards of the hospital to become acquainted with the newer developments in pediatrics.

DEATHS

Dr. Abel Zubizarreta of Buenos Aires, one of the founders of the Argentine Society of Pediatrics, died recently at the age of 65.

CORRECTION

In the abstract of the article by V. Angelini, entitled, "The Inorganic and Acid Soluble Organic Phosphorus of the Blood Serum in Spontaneous and in Experimental Rickets," in the November issue (Am. J. Dis. Child. **48**:1100, 1934), "0.01 mg.," at the end of the third line, should read "1.01 mg."

Abstracts from Current Literature

Pathology, Bacteriology and Biochemistry

Occurrence of Amyloidosis in Rabbits Experimentally Injected with Tuberculosis. R. M. Thomas, Am. J. Path. **10**:419 (May) 1934.

Amyloid degeneration occurred in 52 per cent of 175 rabbits experimentally infected with bovine tubercle bacilli. The occurrence of amyloidosis was restricted to animals surviving longer than two months after infection. The frequency of occurrence was greatest after the eighth month (75 per cent). The organs affected were the spleen, liver and kidneys, the spleen being most frequently affected. There was a uniform tendency for the deposition of amyloid to occur in the animals that showed the most extensive caseation of their lesions.

Author's Summary.

Effect of Morphine on Obstructed Intestine. Alton Ochsner, I. M. Gage and R. A. Cutting, Arch. Surg. **28**:406 (Feb.) 1934.

Because of the widespread use of morphine in surgical practice, the authors studied dogs with obstructed intestines. Observations were made on animals with obstruction of forty-eight hours' duration and with obstruction of seventy-two hours' duration. It was found that opium derivatives stimulate rather than inhibit the activity of the small intestine. From the experimental and clinical observations the authors conclude that the postoperative use of morphine in no way favors ileus. On the contrary, its administration has been beneficial in cases of ileus. They also conclude that the beneficial results obtained from the administration of opiates in cases of peritonitis are not due to the "splinting" of the bowel, but are probably due to the analgesic and sedative properties of the drugs. It was evident to them that morphine is a definite stimulant to intestinal activity and that it can be compared with hypertonic salt solution in its efficacy, although on intestines obstructed for seventy-two hours its effect was less marked than that of the salt solution.

Kaiser, Rochester, N. Y.

Relation Between the Formation of Stones in the Kidney and Bladder and Food. A. Polak, Nederl. tijdschr. v. geneesk. **78**:166 (Jan. 13) 1934.

By adding 3 per cent calcium carbonate to the food of rats fed an adequate diet it is possible to cause stones in the kidney and bladder in nearly 100 per cent of the animals.

van Creveld, Amsterdam, The Netherlands.

Corrected Method for the Determination of Bilirubin. A. A. Hymans, van den Bergh and W. Grotepass, Nederl. tijdschr. v. geneesk. **78**:259 (Jan. 20) 1934.

The authors describe an improvement in the diazotizing method for the determination of bilirubin in the blood serum. The improvement consists in a colorimetric determination with monochromatic light in a suitable instrument, in which a wire gauze which partially excludes light is substituted for the colored liquid which was previously used for comparison, the instrument being calibrated with chemically pure bilirubin. A second improvement is brought about by avoiding adsorption of the bilirubin by the albumin precipitate, which occurs with the original method. This is obtained by treating the serum with a definite amount of reagent and dilute alcohol to which a buffer is added.

van Creveld, Amsterdam, The Netherlands.

FURTHER RESEARCHES ON THE EXCRETION OF UROBILIN AND BLOOD DESTRUCTION. A. LICHTENSTEIN, Nederl. tijdschr. v. geneesk. **78**:1522 (April 7) 1934.

Whereas the average excretion of urobilin in the feces of an average European weighing 70 Kg. amounted to from 135 to 150 mg. daily, in a Javanese weighing 55 Kg., it was only from 75 to 80 mg. This lower rate of excretion was supposed to be conditioned by a food poor in animal protein. In ten healthy vegetarians in Amsterdam the average daily excretion of urobilin was estimated and found to be 75.4 mg. Persons suffering from constipation also showed a markedly lowered excretion of urobilin, the causes of which were investigated.

In consequence one must discard the assumption that by estimating the amount of urobilin excreted one can calculate the average time of survival of the red blood corpuscles in an absolute number of days. However, the blood destruction index, as described by Lichtenstein and Terwen, remains of equal value.

VAN CREVELD, Amsterdam, The Netherlands.

Nutrition

THE EFFECT OF VITAMINS AND THE INORGANIC ELEMENTS ON GROWTH AND RESISTANCE TO DISEASE IN CHILDREN. ALAN BROWN and FREDERICK F. TISDALL, Ann. Int. Med. **7**:342 (Sept.) 1933.

These authors call attention to the fact that at least ten inorganic elements are necessary for life, but that only in the case of calcium, iron and iodine should the supply of these elements not be left to chance. The effect produced by lack of the various vitamins and the sources of the vitamins are discussed. Studies are presented bearing on the importance of these food elements to growth and resistance to infection. A lack of vitamin B complex and also of vitamin D lowered the resistance of rats to infection.

The authors also present evidence to show that, for the first time, dental caries indistinguishable from the human type has been produced in rats and that such caries may be either prevented or cured by adequate amounts of vitamin D and phosphorus in the diet.

Vitamin D in the form of viosterol dissolved in corn oil was added to the shortening used in bread. Such bread is now being produced for sale on the market. A special cereal is advocated, which is rich in the necessary vitamins and inorganic elements, as a means of making these substances further available.

READING, Galveston, Texas.

GASTRO-INTESTINAL ALLERGY IN CHILDREN. HORTON CASPARIS, Ann. Int. Med. **7**:625 (Nov.) 1933.

In this article Casparis considers the gastro-intestinal manifestations which may occur in children as the result of allergy and suggests that they bear a relationship to similar symptoms which occur in adults. Only evidences of local irritation to the gastro-intestinal tract are discussed. The author makes the point that when vomiting is due to allergy it is persistent, and no relief is obtained unless the causative factor is removed completely or partially. Such symptoms as colic, frequent stools containing mucus and the passage of flatus are often the result of allergic manifestations. In another group of patients, abdominal discomfort is the chief complaint. The methods of desensitization are discussed.

READING, Galveston, Texas.

A NEW CUTANEOUS MANIFESTATION IN THE SYNDROME OF VITAMIN A DEFICIENCY. L. J. A. LOWENTHAL and H. KAMPALA, Arch. Dermat. & Syph. **28**:700 (Nov.) 1933.

The authors give the clinical description of a cutaneous lesion along with the histologic studies of the same, as seen in the prisoners at the Uganda Central

Prisons in East Africa. The lesion consisted of dryness of the skin, itching, a papular eruption, folliculitis and some associated acne. The papules were about ¼ inch (0.6 cm.) in diameter, smooth-topped, black and shiny. The edges were sharply demarcated, and the shape of the papules was round or polygonal. They were never as obtuse or coniform as the common acne papule.

It was found that eighty-one, or 8 per cent, of the prisoners were afflicted with one or more of the following conditions: night blindness, xerophthalmia, dermatosis and acne. The numbers suffering from these disorders were 71, 45, 74 and 73, respectively. The routine and diet of these prisoners were unchanged, except for the addition of 1 ounce of cod liver oil daily. Within nine weeks the extent of the cures was: night blindness, 100 per cent; xerophthalmia, 100 per cent, and dermatosis, 98.7 per cent. The authors believe that since the dermatosis improved concurrently with the ocular symptoms on the administration of vitamin A, it was part of the same syndrome.

DULIN, Iowa City.

EXPERIMENTAL VITAMIN (A, B_1, B_2, AND B COMPLEX) DEFICIENCY; HISTOLOGIC CHANGES IN THE CENTRAL NERVOUS SYSTEM. ROY R. GRINKER and ERNESTINE KANDEL, Arch. Neurol. & Psychiat. **30**:1287 (Dec.) 1933.

The effect of vitamin B_1, B_2 and B complex deficiency on the central nervous system was studied because of the inability to prevent or alter the degeneration of the central nervous system in cases of pernicious anemia treated with vitamins. Rats and monkeys were fed vitamin-deficient diets over long periods. The authors concluded that long-standing, severe vitamin B_1, B_2 and B complex deficiency in rats causes no clinical symptoms or histologic changes of a degenerative nature, save for mild nonspecific alterations in the ganglion cells and blood vessels. Long-standing, severe vitamin A deficiency causes no degeneration in the central nervous system of monkeys. The changes in the central nervous system in pernicious anemia are therefore not due to vitamin deficiency.

BEVERLY, Chicago.

AN APPRAISAL OF ANTIRACHITICS IN TERMS OF RAT AND CLINICAL UNITS. A. F. HESS and J. M. LEWIS, J. A. M. A. **101**:181 (July 15) 1933.

Antirachitic milks require a surprisingly small number of rat units (from 35 to 40 daily) to protect or heal, while viosterol requires the largest number of units. Irradiated milk in quantities of from 20 to 24 ounces (590 to 608 Gm.) assures protection and is most desirable because it is automatic, inexpensive and contains calcium and phosphorus as well as the antirachitic factor. The wide differences in activity between the various antirachitic substances indicate that a clinical as well as a laboratory pharmacology must be considered. Therefore, the minimal number of therapeutic units must be determined first and then expressed in terms of rat units.

BONAR, Salt Lake City.

A STUDY OF THE TOTAL AND ULTRAFILTRABLE CALCIUM AND THE ACID SOLUBLE PHOSPHATE CONTENT OF THE BLOOD SERUM OF FOUR HUNDRED AND TWENTY-TWO HEALTHY CHILDREN. M. S. NEEDLES AND C. M. MARBERG, J. Lab. & Clin. Med. **18**:1227 (Sept.) 1933.

This study was undertaken in order to determine whether there is any relation between calcium and phosphorus metabolism and osseous development and the incidence of dental caries. Three hundred and twenty-three children (the test group) were put on the standard Mooseheart diet for one year, and, during a second year, in addition to this diet, were given a pint of orange juice and the juice of one lemon daily. A second group was used as a control. This group consisted of 91 subjects, who were kept on the standard Mooseheart diet. All the children were healthy, and all other conditions of living were identical. The final results showed that there is no relation between the calcium and phosphorus content of the blood serum and dental caries. A summary of the technic is given.

MCMURRAY, Galveston, Texas.

GROWTH PROBLEMS: PART II. BASAL METABOLIC RATE VARIATIONS IN RELATION TO BODY BUILD, ADOLESCENCE AND ALLERGY IN CHILDREN. WILLIAM PALMER LUCAS, HELEN BRENTON PRYOR, CRAWFORD BOST and SAXTON T. POPE, J. Pediat. **3**:856 (Dec.) 1933.

Basal metabolism rates were determined for six hundred and eighty normal children. High basal metabolic rates were found to be characteristic for slenderly built children and low rates for broadly built ones. The basal rate regularly decreases from early childhood to adolescence. During adolescence the rate frequently varies widely both above and below normal at different times in the same person. Children under 10 years of age with minus basal rates tended to put on weight readily and to be sluggish. In the slender children whose basal rates were lower than the average, 68 per cent were allergic. Also, 80 per cent of all the allergic children in this series had minus rates.

LEMASTER, Evanston, Ill.

VITAMINS A AND D: THEIR RELATION TO GROWTH AND RESISTANCE TO DISEASE. ROBERT SUTHERLAND, Brit. M. J. **1**:791 (May 5) 1934.

A dietary survey in Peterhead showed that the diet of many families of the poorest classes was grossly inadequate in several respects and presumably deficient in vitamins A and D. A concentrate of vitamins A and D was therefore administered for six months in daily doses equivalent in vitamin A to rather more than 1 ounce (29.5 cc.) of high grade cod liver oil to 294 school children of the lower working classes in Peterhead; 281 contemporaries acted as controls.

The rate of growth of the treated children appeared to be only slightly better than that of the controls, while susceptibility to infection and resistance to established disease were apparently unaffected by the treatment.

Evidence is produced to suggest that the cause of this failure lay in the fact that the vitamin supplements supplied only one dietary deficiency and left uncorrected associated deficiencies of equally essential constituents of the diet. The importance of a well balanced dietary is stressed, and the value of supplementing the diet with milk, as a step in this direction is compared favorably on both biologic and economic grounds with that of adding vitamins.

ROYSTER, University, Va.

MAGNESIUM DEFICIENCY IN THE RAT. RONALD W. BROOKFIELD, Brit. M. J. **1**:848 (May 12) 1934.

Convulsive phenomena occurring in rats deprived of magnesium are described. The cutaneous changes reported by other workers were not observed, but acute degenerative changes were present in the liver and kidneys.

ROYSTER, University, Va.

OBSERVATIONS ON THE VISUAL FIELDS IN VARIOUS FORMS OF VITAMIN A DEFICIENCY. S. M. KIANG, Nat. M. J. China **18**:827 (Oct.) 1932.

In six cases of vitamin A deficiency of various forms and severity there was found concentric contraction not only of the blue field but also of the red and white fields. In two of the cases there was inversion of the blue and red fields on admission and then intersecting of the blue and red fields; finally the blue field became larger than the red field. In two other cases there was intersecting of the blue and red fields on admission, and then the blue field became larger than the red field, while in the remaining two cases there was inversion of the blue and red fields on admission, and intersecting of these fields on discharge. The length of the time from the intersecting of the blue and red fields to the point at which the blue field became larger than the red was ten days. In view of the clinical symptoms, no definite relationship between the changes in the visual fields, on the one hand, and the clinical symptoms, on the other, can be expressed and figured, but as a whole the contraction of the color fields, especially of the

blue field, is proportional to the other clinical symptoms of vitamin A deficiency, and therefore the changes of the color fields may be regarded as one of the main symptoms of the eye in vitamin A deficiency in adults.

McKee. [Arch. Ophth.]

Action of Carbonic Acid on Blood Sugar. D. Cordier, Ann. de physiol. **10**:1, 1934.

Anesthetized dogs were allowed to inhale increasing concentrations of carbonic acid, but with normal amounts of oxygen. Progressively increasing hyperglycemia occurred, which was accompanied by a parallel increase in the carbon dioxide combining power of the plasma and a parallel and progressive decrease in the p_H.

An attempt was made to dissociate the possible factors causing the hyperglycemia. Intravenous injections of sodium bicarbonate in concentrations high enough to cause the carbon dioxide combining power to be more than 100 volumes per cent caused practically no change in the blood sugar. Slow injections of hydrochloric acid given intravenously or into the lumen of the intestines caused progressive decrease of the total carbonic acid and of the p_H of the blood, but did not cause hyperglycemia, even when the acid intoxication caused death. The rapid intravenous injection of massive doses of hydrochloric acid caused sudden changes in the acid-base equilibrium and resulted in hyperglycemia. Acidosis caused by the inhalation of carbon dioxide brings about changes in the reaction of the tissues which a fixed acid cannot accomplish.

The authors believe that if one holds to the theory that hyperglycemia caused by acids is due to acceleration of glycogenolysis in the hepatic cells, one must admit that the special action of carbonic acid, as compared with that of other acids, is due to its great diffusibility in the cells. It might easily modify the reaction of the interior of the hepatic cells and activate glycogenolysis.

Budson, Detroit.

The p_H of the Stools of Infants Suffering from Digestive Disturbances and Subjected to Dietary Treatment. Axente Iancou and Malevanaia-Sorescou, Bull. Soc. de pédiat. de Paris **30**:703 (Dec. 20) 1932.

Determinations of the p_H of the stools of ten groups of infants were made. The figures varied a great deal. The greatest acidity, an average of 5, was obtained in the group that received breast milk only. The greatest alkalinity, an average of 7.4, was found in those who were fed almond milk and breast milk in the proportion of 5:1. No conclusions are drawn from the results of this study.

Benjamin, Montreal, Canada.

A Probable Case of Latent Avitaminosis of Ribadeau-Dumas Type. M. Schachter, Bull. Soc. de pédiat. de Paris **30**:718 (Dec. 20) 1932.

A boy, aged 6 months, had a large abdomen and was markedly constipated and irritable. These symptoms had been present for about two weeks. The diet was not changed, but cooked vegetables were added, and he was given a preparation containing vitamins A and D. One week later he had one or two normal stools daily; the irritability had disappeared, and the abdomen soon returned to the normal size for his age. The case is viewed as being probably similar to a number of cases described by Ribadeau-Dumas, in which there was vitamin B deficiency, although no food particularly rich in vitamin B was used in the treatment.

Benjamin, Montreal, Canada.

Nutritional Upsets in Childhood. Eugen Stransky, Paidoterapia **12**: 7 (May) 1933.

Anorexia in childhood is caused not by nutritional troubles due to disorder of the metabolism but by a prejudice against the *milieu*, a desire to evade the

obligation to eat, the resistance and the neuropathic condition of the child. A radical change of the *milieu* for a long time will bring about a complete cure.

Periodic vomiting associated with acetonuria appears to be a neurosis the cause of which is unknown. Von Gierke's disease and Christian's syndrome are common metabolic disturbances in childhood. In the first the liver is greatly enlarged, owing to the accumulation of glycogen, which is also later stored in other parts of the body. Notwithstanding, the blood sugar is reduced, and the body is continually in a state of carbohydrate shortage, as the glycogen depots cannot be mobilized. Christian's syndrome belongs to the lipoid disturbances, as do Gaucher's disease and Niemann-Pick disease. The cholesterol metabolism is at fault.

Acute diarrhea is effectively treated by a diet of raw apples. Celiac disease is discussed in regard to its symptomatology, etiology and the banana treatment.

HERRON, Spokane, Wash.

BASAL METABOLISM IN INFANTS AND CHILDREN. BÉLA SCHICK and ANNE TOPPER, Paidoterapia **12**:95 (June) 1933.

During the past decade, much has been added to the knowledge of the basal metabolism of children, and the technic used in measuring the rate has been so simplified that it can be used even in the physician's office.

A history of the early investigations is given. It is to Lavoisier that one owes the birth of the science of metabolism. To Germany one owes the painstaking work of the Voit school and to America the perfection of method and standard and the simplification of detail and technic.

Basal metabolism is the amount of heat produced as a by-product of the chemical activity of the body. It is measured in the postabsorptive state. The mechanism by which it is measured is described in detail:

The basal metabolic rate is increased 14 per cent during the prepuberal period (Dubois). This increase continues until puberty is established and is physiologic. The rate increases according to the physiologic age and thus appears more rapidly in girls than in boys. The basal metabolism is affected by age, sex, size, youth, growth and development, puberty, diet, muscular activity, nervous and physical tensions of living and, possibly, race.

The basal metabolic rate is increased in the diabetic child. The greatest increase found in diabetic children was +21 per cent in girls from 15 to 17 years of age; this increase was due to the fact that diabetic girls do not reach puberty until about this age. The basal metabolic rate is lowered in premature infants, because of the lowered body temperature and the incomplete development of the organs and thus a decrease in their normal functioning. The rate may be affected by drugs (narcotics and sedatives), fever, infection, abnormal nutritional states and other diseased conditions.

While studies of the basal metabolic rate are valuable as a clinical aid in diagnosis and treatment, they are only laboratory tests and must not be accepted blindly.

HERRON, Spokane, Wash.

THE PASSAGE OF VITAMIN A INTO MILK. H. FASOLD and H. PETERS, München. med. Wchnschr. **80**:1427 (Sept. 15) 1933.

It is difficult to determine slight vitamin deficiency in an infant during the first few months of life. Many clinical observations and experimental studies have shown that such a deficiency may produce injuries which cannot be corrected by later addition of vitamins. It is possible that, owing to a latent vitamin deficiency in infancy, a tendency to chronic injuries is developed. When an animal is given just sufficient vitamin A to maintain normal growth, it is more susceptible to infection than control animals given a larger ration of vitamin A.

Human milk is deficient in both vitamins A and D. Fasold and Peters fed lactating rats a potent vitamin A product in addition to a balanced diet. Control animals received the same diet without additional vitamin A. The nursing rats

fed by the mothers receiving additional vitamin A grew more rapidly than those fed by the control mothers.

A growing organism has a high vitamin requirement. During pregnancy and lactation a mother may be considered a growing organism. Many mothers today must eat margarine, lard or, at best, butter made from "winter" milk, all of which are deficient in vitamin A. The main source of vitamin A is carrots, which does not supply the quantity needed. One way to supply the extra quantity of vitamin A to the mother and nursing infant is to add it to the mother's diet in the form of cod liver oil or one of the cod liver oil concentrates.

BRAHDY, Mount Vernon, N. Y.

A CASE OF HEMIHYPERTROPHIA. J. H. SMIDT VAN GELDER, Maandschr. v. kindergeneesk. **3**:39 (Oct.) 1933.

A case of this disease is reported in a girl, aged 3 years.

VAN CREVELD, Amsterdam, The Netherlands.

ACIDOSIS IN CHILDHOOD. J. C. SCHIPPERS, Maandschr. v. kindergeneesk. **3**:145 (Jan.) 1934.

A short discussion of the different forms of acidosis in childhood is presented, and three cases of severe acidosis in children aged 2, 1½ and 9 years, respectively, are reported.

VAN CREVELD, Amsterdam, The Netherlands.

KETOGENIC DIET. J. M. SOETERS, Maandschr. v. kindergeneesk. **3**:161 (Jan.) 1934.

This article consists of a discussion of the application of the ketogenic diet and a number of recipes.

VAN CREVELD, Amsterdam, The Netherlands.

GASEOUS METABOLISM IN CHILDHOOD. M. DE BRUIN, Nederl. tijdschr. v. geneesk. **77**:5684 (Dec. 23) 1933.

In ninety-nine children with a body weight greater than 24 Kg. the basal metabolism was determined by means of the apparatus of Dusser de Barenne and Burger. The results were plotted in curves, which gradually joined the curves of standard values already existing for Dutch children weighing less than 24 Kg.

The determination of basal metabolism with the help of the standard curves for body weight seems the most reliable method for general use. It should, however, be borne in mind that the fatty tissue is inactive in the production of heat, and this often makes correction of the figures for the weight necessary. In children whose body weight shows greater deviations from the normal, the basal metabolism should be judged according to the ideal weight plus 3 Kg. for fat children and minus 3 Kg. for thin children.

VAN CREVELD, Amsterdam, The Netherlands.

LUNGS AND VITAMIN D. G. A. METZ, and P. A. COPPENS, Nederl. tijdschr. v. geneesk. **78**:769 (Feb. 17) 1934.

Research as to the fate of orally administered viosterol in the dog has demonstrated, among other things, that this substance is destroyed by the lungs.

VAN CREVELD, Amsterdam, The Netherlands.

Prenatal Conditions

CONGENITAL COMPLETE HEART-BLOCK. M. CAMPBELL and S. S. SUZMAN, Am. Heart J. **9**:304 (Feb.) 1934.

Over a period of six years the authors encountered eight cases of congenital complete heart block. As they were able to find reports of only forty-five cases, they believe that the condition is frequently overlooked.

The criteria used in determining the congenital nature of the heart block were a slow pulse at an early age, signs of congenital morbus cordis, the absence of any history of infection and the occurrence of syncopal attacks in infancy or early childhood. In all eight cases the presence of complete heart block was confirmed by electrocardiograms. Some patients also showed frequent extra systoles.

In all cases physical signs were present to suggest congenital heart disease, which was thought in most instances to be due to a defect of the interventricular septum. No patient had morbus caeruleus.

In the fifty-three cases studied, nine patients died. Four died in early infancy, probably because of the associated congenital malformations. One died of bacterial endocarditis. Four others died suddenly, three of whom had serious congenital heart disease as well as heart block. One patient in apparent good health died suddenly at the age of 13 years, possibly owing to an attack of Stokes-Adams disease. Hence the prognosis seems to depend chiefly on the seriousness of the cardiac malformation rather than on the presence of heart block.

STANLEY GIBSON, Chicago.

MALFORMATION OF THE HEART OF THE NEW-BORN. GRETE STOHR, Arch. Path. **17**:311 (March) 1934.

Two cases of malformation of the heart secondary to fetal inflammation are reported. The absence of developmental anomalies in any other organs, the absence of a family history of congenital defects, the situation of the anomaly in the left side of the heart, complete development of the interventricular septum and, finally, the histologic observations support the belief that the malformations were due to inflammatory reactions during fetal life.

LEMASTER, Evanston, Ill.

DEATH OF FOETUS IN UTERO. A. L. DIPPEL, Bull. Johns Hopkins Hosp. **54**:24 (Jan.) 1934.

The incidence of fetal death *in utero* during the last trimester of pregnancy in a series of 25,000 consecutive deliveries was 306, or 1.2 per cent. The incidence is higher in the colored than in the white race, with a ratio of 2.6:1. The age of the mother has no influence on death *in utero,* although the incidence increases with multiparity. The majority of intra-uterine deaths occur some weeks before the estimated date of confinement. Patients with acute toxemia of pregnancy usually fall into labor soon after the intra-uterine death of the fetus, while the duration of retention following fetal death due to other causes is usually longer. More males than females die *in utero,* the ratio being 125.

The signs and symptoms of fetal death *in utero* are usually clearcut and consist in failure of the mother to feel fetal movements, cessation of the fetal heart beat, absence of normal fetal body tone, a boggy fetal head, crepitation of the fetal skullbones and retrogressive changes in the size of the uterus. Further suggestive signs and symptoms which often occur are: maternal nausea, malaise, headaches, foul breath, a bad taste in the mouth, hyperactivity of the fetus followed by cessation of fetal movements, a pronounced uterine souffle, a fall in the basal metabolic rate and retrogressive changes in the breasts. Adjuncts helpful to diagnosis, but not altogether reliable or pathognomonic are the Aschheim-Zondek test and roentgenograms. Acetonuria is not a constant finding. The clotting time of the maternal blood would seem to be of no value.

The causes of intra-uterine death in order of their frequency were: syphilis; toxemia of pregnancy; loops of cord about some fetal part; intercurrent maternal disease; acts of violence to the abdomen of the mother; the induction of labor; hemorrhage; fetal anomalies; true knots in, and torsion of, the umbilical cord; unusual shortness of the cord; localized constriction of the cord; incarceration of the uterus, and uterine anomalies. Male fetuses seem to be more susceptible to syphilis and succumb to it more readily than do female fetuses. The gross maternal mortality in the series was 0.12 per cent, and the corrected mortality 0.06 per cent.

The morbidity rate was high—23.25 per cent, as contrasted with 17.75 per cent for the general clinic population. It is seldom necessary, from the standpoint of the patient, to induce labor because of fetal death *in utero*, and rarely, if ever, necessary to effect a hasty delivery.

The labor pains were not significantly different from those of a patient with a living fetus. The incidence of postpartum hemorrhage was lower in the cases of intra-uterine death than in the general clinic. Abnormal presentations, such as breech, transverse and compound, occur more frequently following death of the fetus *in utero*. Except when death is due to syphilis or nephritis, there seems to be no increased chance of a second premature fetal death *in utero* for the patient.

THE USE OF OXYGEN IN THE CARE OF FEEBLE PREMATURE BABIES. WILLIAM P. BUFFUM and GEORGE F. CONDE, J. Pediat. **4**:326 (March) 1934.

This report deals with three premature infants who were apparently in poor condition, but who improved strikingly when placed in an oxygen box.

LEMASTER, Evanston, Ill.

ACHONDROPLASIA IN A TWIN. ABRAHAM BROOKNER, J. Pediat. **4**:352 (March) 1934.

A case of typical achondroplasia in one of twin girls, 10 months old, is reported. Excellent photographs of both infants are reproduced.

LEMASTER, Evanston, Ill.

REPORT OF THREE CASES OF CONGENITAL HEART-BLOCK WITH A RÉSUMÉ OF THE LITERATURE TO DATE. LUVERN HAYS, J. Pediat. **4**:380 (March) 1934.

In 1929, Yater reviewed the literature on congenital heart block and collected thirty instances. The author reviews nine cases published since then and reports three cases from his own observations. All the patients appeared to have congenital heart disease, and the most probable defect in each case was an imperfect ventricular septum. This lesion is likely to be associated with imperfect development of the atrioventricular conduction system. The electrocardiographic tracings from the authors' three cases are reproduced.

LEMASTER, Evanston, Ill.

CONGENITAL HEART DISEASE. SIDNEY D. LEADER and M. A. KUGEL, J. Pediat. **4**:595 (May) 1934.

A case of congenital stenosis of the conus of the right ventricle complicated by valvular stenosis of inflammatory origin is described. There were healed rheumatic endocarditis and fresh subacute bacterial endocarditis in addition to the original congenital malformation.

LEMASTER, Evanston, Ill.

CONGENITAL HEART DISEASE INCLUDING REPORT OF A CASE OF CONGENITAL HEART-BLOCK WITH AUTOPSY FINDINGS. WILLIAM G. LEAMAN, M. Clin. North America **17**:853 (Nov.) 1933.

A male infant cried feebly and became extremely cyanotic immediately after birth. The heart was enlarged. The first sound was obscured by a blowing systolic murmur and a second weak sound. The murmur was heard all over the chest and was loudest over the second interspace on the left. The heart rate was 40 beats per minute. Electrocardiograms showed complete heart block. After the administration of atropine there was some increase in the frequency of the heart rate, and many premature ventricular beats appeared. The infant died within a few hours. At autopsy both auricles and both ventricles were found to be abnormal in shape. The interventricular septum was defective in its upper third, and the defect extended upward to involve almost the whole of the interauricular septum. While it is assumed that the heart block was the result of the involve-

ment of the conducting fibers in the septal defect, serial sections were made. In other reported cases of defective septum surprisingly few changes have been found in the distribution of the bundle.

EUGENE SMITH, Ogden, Utah.

CONGENITAL SCOLIOSIS. SPENCER SILVERSTEIN and PHILIP VIVIRITO, M. J. & Rec. **239**:167 (Feb.) 1934.

Four normal physiologic types of curvature of the spine are recognized: (1) the forward cervical, (2) the backward dorsal, (3) the forward lumbar and (4) the backward sacrococcygeal. Scoliosis is divided into two classes: (1) the idiopathic class and (2) the congenital and acquired class. Dorsal scoliosis is described, and a case is reported of congenital dorsal scoliosis in a child, aged 4 years.

The best method of determining scoliotic involvement is roentgenography. The treatment which was carried out in the case reported is described.

WILLIAMSON, New Orleans.

CONGENITAL ATRESIA OF THE ESOPHAGUS. L. T. PERRAULT and H. J. BURMAN, New York State J. Med. **33**:1092 (Sept. 15) 1933.

A child, 9 months of age, had an obstruction due to a "congenital membrane" 12 cm. from the alveolar margin. It was successfully treated by dilation.

AIKMAN, Rochester, N. Y.

CONGENITAL CHRONIC DUODENAL OBSTRUCTION WITH PERITONEAL BANDS. FRANCES BRAID, Proc. Roy. Soc. Med. **26**:1540 (Oct.) 1933.

A boy, aged 4½ years, had suffered from frequent attacks of vomiting from early infancy. If he swallowed food, he vomited immediately. Roentgen examination showed one-third residue of meal in the stomach after ten hours. Laparotomy revealed a large stomach with a normal pylorus and long first and second parts of the duodenum causing a kink in the duodenum itself and at the duodenojejunal flexure. The bands were divided.

The condition improved slowly until after six years. This improvement corresponds to the spontaneous improvement noted at about this age in the arteriomesenteric group of cases of duodenal obstruction. From this it would seem that the peritoneal bands were only partly responsible for the obstruction.

WILLIAMSON, New Orleans.

MONGOLISM AND ACHONDROPLASIA IN TWIN BROTHERS. E. P. LAPAGE, Proc. Roy. Soc. Med. **27**:115 (Dec.) 1933.

The mother of twin boys, one with mongolian idiocy and the other with achondroplasia, was a young primipara, who was healthy except for high blood pressure. The mongolian idiot died at the age of 5½ months of bronchopneumonia, and the child with achondroplasia died a short time after of the same malady. Photographs of the twins and roentgenograms of the long bones of the child with achondroplasia are included in the report.

WILLIAMSON, New Orleans.

Acute Infections

THE IMPORTANCE OF IMMUNIZATION IN THE CONTROL OF ACUTE CONTAGIOUS DISEASE. HUBERT S. HOUSTON, Illinois M. J. **65**:161 (Feb.) 1934.

Effective measures for the control of transmissible disease have developed within a comparatively recent period. The consideration of immunization involves statistics covering a period of years and also other pertinent factors having to do with the control of disease. Records of the army, alone, establish the importance of immunization in the control of smallpox and typhoid fever. Steady progress has been made in the control of diphtheria, especially during the past ten years. The

use of plain and precipitated toxoid leaves little to be desired. Scarlet fever toxin undoubtedly has immunizing value, but certain factors are at present retarding the progress of further developments. The possibilities for the employment of scarlet fever toxoid seem favorable. Immunization against whooping cough is a debated question, but authentic favorable reports have been published. The subject needs further study. More general employment of dependable specific measures would gradually modify quarantine regulations.

BARBOUR, Peoria, Ill.

VACCINATION AGAINST WHOOPING COUGH. T. MADSEN, J. A. M. A. **101**:187 (July 15) 1933.

The difference of opinion regarding the value of vaccination for pertussis is probably due to some extent to the lack of distinction between therapeutic and prophylactic properties of the vaccine and to the lack of suitable controls. Such a control material is found in the Faroe Islands. The results of two large epidemics showed that in the vaccinated group there were one-sixteenth less deaths than in the nonvaccinated group, and the course was milder and shorter. The favorable results may be attributed to the facts that the vaccine was made from young strains; the dose was large (total, 22,000 million), and the vaccination was completed shortly before the onset of the epidemic, when the titer of the antibody produced by the vaccine was highest.

BONAR, Salt Lake City.

ACTIVE IMMUNIZATION AGAINST DIPHTHERIA. H. W. STRAUS, J. A. M. A. **101**: 192 (July 15) 1933.

A single intramuscular injection of diphtheria toxoid incorporated in hydrous wool fat actively immunized 99 per cent of one hundred and three patients within two months. In most cases immunity developed within three or four weeks, and in one case within two weeks. Because of the early development of active immunity, this preparation should be useful in checking epidemics.

BONAR, Salt Lake City.

STUDIES ON MENINGOCOCCUS INFECTION: V. THE PRESENCE OF MENINGOCOCCUS PRECIPITINOGENS IN THE CEREBROSPINAL FLUID. GEOFFREY RAKE, J. Exper. Med. **58**:375 Sept.) 1933.

In studies III and IV in this same journal the author, with a co-worker, described a type-specific substance found in the autolysates of the different strains of meningococci—types I, II, III and IV—and suggested the relationship of this substance to certain serologic phenomena. In the present study (V), after having obtained monovalent rabbit serum prepared against each of the four strains, he shows the results of precipitin tests on the spinal fluid in twenty-three cases of meningococcic meningitis and on the spinal fluids in eight cases of other forms of cerebrospinal disease. He concludes in part that the reaction offers an easy and rapid method of ascertaining to which type of meningococcus a particular case of meningitis is due and facilitates the immediate use of a monovalent therapeutic antimeningococcal serum. Negative results are secured when the spinal fluid is obtained after the beginning of intrathecal serum treatment and also occasionally when the number of infecting organisms is small. In other diseases of the meninges and central nervous system the spinal fluid fails to give any precipitin reaction with the monovalent serums.

LUECKE, Dallas, Texas.

BACTERIOLOGIC AND SEROLOGIC STUDY OF 89 CASES OF DYSENTERY IN WHICH B. DYSENTERIAE FLEXNER AND B. DYSENTERIAE SONNE (B. DYSENTERIAE CASTILLANI-SONNE) WERE ISOLATED AS THE CAUSATIVE AGENTS. N. H. SOULE and A. M. HEYMAN, J. Lab. & Clin. Med. **18**:549 (March) 1933.

During the period from July 1930 to January 1931 eighty-nine cases of dysentery were studied. Sixty-seven of the patients were hospitalized, and twenty-two were

cared for at home. Dysentery bacilli were recovered from sixty of these patients. The work indicated that the organisms fell into two groups and that the epidemic was due to these specific organisms. The two groups of organisms were Bacillus dysenteriae Flexner and Bacillus dysenteriae Sonne. A complete account is given of the technic used in this study and of the characteristics of the strains of organisms isolated.

McMURRAY, Galveston, Texas.

FURTHER OBSERVATIONS UPON THE COMPLEMENT FIXATION TEST IN THE DIAGNOSIS OF AMEBIASIS. C. F. CRAIG, J. Lab. & Clin. Med. **18**:873 (June) 1933.

Persons harboring Entamoeba histolytica—whether carriers or patients showing clinical symptoms—show a complement-fixation reaction. Normal persons or persons infested with other amebae do not show a positive reaction. After cure of a case of infestation with Entamoeba histolytica the reaction becomes negative within from three to twenty-eight days. In cases in which there is a relapse the reaction is negative during the period of remission, but becomes positive even before the amebae appear in the stools. The test is of great value in the diagnosis of abscess of the liver caused by Entamoeba histolytica, in determining carriers, in mild and atypical cases and in the control of treatment.

McMURRAY, Galveston, Texas.

CEPHALOTETANUS WITH A FACIAL PARALYSIS. CHARLES M. GRAY, J. Missouri M. A. **31**:139 (April) 1934.

While cephalotetanus is not rare as a complication of dirty wounds of the head, associated facial paralysis is unusual.

The paralysis is of the type of Bell's palsy, involving the muscles controlling the forehead, eyelids, cheek and mouth. There is usually also trismus of the masseters, preventing complete or partial opening of the jaws. In the few cases in which recovery was reported the paralysis cleared up slowly but completely.

A case is reported in this article in which cephalotetanus was complicated by initial facial paralysis.

The various methods of treating tetanus are reviewed, the one giving theoretically the most promise being that of supersaturating the blood with the antitetanic serum by continuous intravenous administration. A case in which continuous intravenous administration of 705,000 units of the serum was required to produce visible improvement was reported by Silverthorne and Hart. Other methods mentioned are the intensive use of the serum, the use of magnesium sulphate and the use of phenol in a dilution of 1:400, as suggested by Suvansa.

BERGER, Kansas City, Mo.

A NEW PERTUSSIS ANTIGEN. J. M. FRAWLEY, M. STALLINGS and V. C. NICHOLS, J. Pediat. **4**:179 (Feb.) 1934.

Recently isolated strains of Haemophilus pertussis are grown on mediums of human blood, washed in a buffered isotonic solution and mechanically disrupted in a special type of ball mill. The resultant suspension is subjected to ultrafiltration through membranes of acetic collodion of such porosity that all intact cells are retained, while material in solution or in a finely dispersed phase passes through. The water-clear filtrate contains those constituents of the live cell put into solution or suspension by physical rupture of the cell membrane and is free from cell metabolites and products of denaturation or degradation resulting from heat or chemical treatment of the bacteria.

The results of treatment with this antigen during an epidemic of whooping cough are discussed and indicate evidence of the protective value of the antigen, although protection is not absolute. Daily injections of 0.1 cc. given intracutaneously and 0.1 cc. subcutaneously are used, the subcutaneous dose being gradually increased until 1 cc. is given.

LEMASTER, Evanston, Ill.

THE IMMUNIZATION OF SCHOOL CHILDREN AGAINST WHOOPING COUGH. J. M. FRAWLEY, J. Pediat. **4**:184 (Feb.) 1934.

The author used a special pertussis antigen consisting of the endocellular element of Hemophilus pertussis extracted by mechanical disruption of the cells and ultrafiltration. The filtrate was diluted to contain the extract of from 7,000,000,000 to 9,000,000,000 organisms in each cubic centimeter.

Four injections were given weekly to 345 school children, while 614 children were not treated and served as controls. During the three months which followed the injections, 12 per cent of the treated group and 10 per cent of the untreated group contracted whooping cough. However, the disease was definitely much milder in those who had received the injections. Further study is being made with increased doses.

LEMASTER, Evanston, Ill.

PERTUSSIS. SALMEN K. SIEBLER and SAMUEL O. KRENT, J. Pediat. **4**:188 (Feb.) 1934.

Intracutaneous injections of fresh Bordet-Gengou's bacilli in physiologic solution of sodium chloride were given to one hundred and eighty-six children. An area of redness of more than 1 cm. in any diameter was considered a positive reaction. In this series 80 per cent of those who had not had pertussis according to the history showed positive reactions, while 76.4 per cent who had had the disease did not react. The test was found to be of value in determining whether exposed children were immune or susceptible.

LEMASTER, Evanston, Ill.

BRUCELLA INFECTION IN CHILDREN. ANGUS MCBRYDE, N. C. DANIEL and M. A. PASTON, J. Pediat. **4**:401 (March) 1934.

Agglutination and intracutaneous tests were made on 210 children in an orphanage who had been drinking milk infected with Brucella organisms for at least five months and in some cases as long as six years. Of the intracutaneous tests, 13 per cent gave definitely positive results, and in 3 per cent the results were questionable. Of 48 children who had stopped drinking infected milk three weeks previously, the agglutination reaction was positive in 7, but two months later they lost their agglutinins. A second group of 164 children was tested by the agglutination test from six to twelve weeks after they had ceased drinking infected milk, and none of them showed agglutinins. A positive intracutaneous reaction indicates the ingestion of some variety of Brucella melitensis at a previous date, but not necessarily a clinical infection. A negative intracutaneous reaction, as well as a negative agglutination reaction, does not eliminate the possibility of a clinical infection.

LEMASTER, Evanston, Ill.

INFECTION AND IMMUNITY. JOHN A. TOOMEY, J. Pediat. **4**:529 (April) 1934.

In this critical review the author discusses his subject matter under the following headings: infection, immunity, hypersensitiveness as a result of passive immunity and the application of the principles of infection and immunity to specific diseases.

LEMASTER, Evanston, Ill.

COMMON CONTAGIOUS DISEASES. PHILIP M. STIMSON, M. J. & Rec. **139**:68 (Jan. 17) 1934.

It is surprising to find such an amount of acurate information about the contagious diseases in the writings of centuries ago. For instance, Hippocrates, about 400 B. C., wrote a good description of several cases of mumps. Von Rosenstein, in 1765, in an article on whooping cough, came astonishingly close to the conception of bacterial infection. Such diseases as whooping cough, measles, diphtheria, scarlet fever, chickenpox and poliomyelitis are discussed.

WILLIAMSON, New Orleans.

A Study of Secondary Cases of Scarlet Fever. William H. Best, New York State J. Med. **33**:881 (July 15) 1933.

A study was made by the Department of Health of New York City to ascertain whether the isolation period of thirty days for scarlet fever is too long. Eleven thousand, three hundred and fifty-seven cases were reviewed, together with 37,788 contacts with these cases. Only 901, or 2.4 per cent, of the patients who came in contact with scarlet fever contracted the disease, and in 56 per cent of these the disease began within one week after the primary case. It is well shown that the quarantine of thirty days, based on the obsolete theory of the infectivity of desquamation, could well be discarded and that twenty-one days is a sufficient period of quarantine for uncomplicated cases of scarlet fever. Patients with complicated cases should be isolated until the complication has cleared up. Longer quarantine causes serious loss of time to all concerned.

Aikman, Rochester, N. Y.

Current Prevalence of Communicable Diseases in the United States, Pub. Health Rep. **49**:357 (March 16) 1934.

For the period of Jan. 28 to Feb. 24, 1934, the incidence of measles was considerably above the usual seasonal expectancy. There were 94,484 cases reported, which is more than twice the number for the last six years. All areas shared in this. The number of cases of scarlet fever reported for the period was 24,249, which is also the highest in six years.

The average mortality from all causes was 12.7 per thousand.

Sanford, Chicago.

Current Prevalence of Communicable Diseases in The United States. Pub. Health Rep. **49**:475 (April 13) 1934.

For the period of Feb. 25 to March 24, 1934, the number of cases of measles rose to 129,505, which is the highest incidence for this period in recent years. All other diseases kept a low level, except poliomyelitis, which with 73 cases showed an incidence 45 per cent higher then in 1933. The average mortality was 12.8 per thousand.

Sanford, Chicago.

Immunity in Infants to Infectious Diseases: Placental Antibodies. Charles F. McKhann and Harriett Coady, South. M. J. **27**:20 (Jan.) 1934.

The authors found that extracts of placental protein contained substances, presumably antibodies, which neutralized diphtheria toxin, blanched scarlet fever rashes, neutralized the virus of poliomyelitis and prevented measles in exposed susceptible patients.

Although the amount of diphtheria antitoxin in the extract is small and probably entirely inadequate to be of clinical value, the measurement of the content of diphtheria antitoxin could be made readily in animals, and thus determinations of the content of diphtheria antitoxin of various lots gave some evidence of the potency and degree of concentration.

Tests of the neutralizing capacity of diphtheria toxin revealed that, although there was some antitoxin in the euglobulin fraction, there was more in the pseudoglobulin fraction. The pseudoglobulin fraction contained blanching substance for scarlet fever rashes; this was almost lacking in the euglobulin fraction. Placental extract did not produce blanching of simple erythemas, heat rashes or drug rashes. The extract was also found to contain an antistreptolysin.

In experiments on monkeys, neutralization of the virus of poliomyelitis was obtained with the earlier preparations in each of three lots tested. The presence of the neutralizing substance in the purified pseudoglobulin fraction was demonstrated in each of four lots subjected to this test.

Placental extract was used in more than one hundred children for the prevention or modification of measles. In ninety-five nonimmune patients exposed to measles in the course of hospitalization for other causes, the extract was administered early in the period of incubation in order to prevent the disease. Ninety-one patients did not contract the disease. No patient contracted the typical disease. Four children who had modified measles were among the earlier patients treated, before any standardization of placental extract had been secured.

The factors which influence the effectiveness of the serum in the prophylaxis or modification of measles are: (1) the time of injection, (2) the dose and (3) the potency of the material.

SCHLUTZ, Chicago.

SCARLET FEVER. T. M. BARBER, West Virginia M. J. **30**:209 (May) 1934.

The author prefaces his article with the statement that his remarks are not original, but gleaned from the best authors.

Scarlet fever is defined. There is a specific cause for scarlatina—Streptococcus scarlatinae—and a specific serum for the prevention and treatment of this condition.

Scarlet fever is less readily communicable than any of the other infectious diseases and would merit less consideration, were it not for its complications, which occur in 40 per cent of the cases and are generally serious.

Any one or more of the common infectious diseases may develop during the course of scarlet fever; of these, diphtheria is the most frequent.

Every case of scarlatina should be treated seriously, as even the mildest may become malignant.

The Schultz-Charlton and the Dick tests are discussed, positive information being attributed to each.

The merits of "scarlet fever serum" for both prevention and treatment, the dose, reactions, results, sensitization and methods of administration are discussed.

Commercial packages of all preparations are shown and the prices are given.

SHAWKEY, Charleston, W. Va.

SCARLET FEVER IMMUNIZATION WITH A SCARLET FEVER TOXOID. GILBERT DANIEL, West Virginia M. J. **30**:212 (May) 1934.

The author describes briefly the detoxified scarlet fever toxin (toxoid), as prepared by Veldee of the United States Public Health Service, and reports his experience with it in a series of 255 patients varying in age from 1 to 44 years.

This toxoid is given in three doses of 0.1, 0.5 and 1 cc. at intervals of three weeks. When it was given in larger doses, even at longer intervals, there were unpleasant reactions.

In 28 preschool children there were mild local reactions, but no constitutional reactions. In 191 school children there were systemic reactions in 5 cases. Of 36 persons (aged from 14 to 44 years), 10 showed marked systemic reactions.

It was not possible to carry out Dick tests at later dates in this series, but Veldee has reported 87.3 per cent negative Dick reactions in 1,700 cases after periods of from four to twenty-eight months. This compares favorably with about 81 per cent negative Dick reactions following five doses of commercial scarlet fever toxin.

SHAWKEY, Charleston, W. Va.

BILATERAL PAPILLITIS FOLLOWING ANTIRABIC INOCULATION: RECOVERY. H. S. CORMACK and L. A. ANDERSON, Brit. J. Ophth. **18**:167 (March) 1934.

A healthy normal woman was bitten on the arm by a dog which was certified rabid on March 3, 1932. She was given 5 cc. of a 5 per cent phenolized sheep vaccine for fourteen days, receiving in all 3.5 Gm. of mixed virus of killed sheep. No untoward symptoms were observed during the treatment, which terminated March 18, 1932.

Nine days later the sight of the right eye, and three days later the sight of the left eye, began to grow dim. Vision of the right eye equaled 6/36, and the left eye was blind. Both eyes showed papillitis. At the end of two weeks the sight gradually returned, and at the end of two months vision and the fields were normal, except for a small centrocecal absolute scotoma. One year later the fundus and vision were normal, but the scotoma persisted.

The authors state that there seems to be no reason to suppose that the optic nerve should necessarily be exempt from attack by a disease the incidence of which is so widespread in the nervous system. ZENTMAYER. [ARCH. OPHTH.]

THE OCCURRENCE OF DIPHTHERIA IN IMMUNIZED PERSONS. J. C. SAUNDERS, Irish J. M. Sc., November 1933, p. 611.

Seventy-eight cases of diphtheria occurred in 6,878 completely immunized children and 1,149 partially immunized children. Thirty-three of these were not confirmed in the hospital. In 18 either the toxoid treatment was not completed or the latent period had not expired. Diphtheria was reported in 7 children who had negative Schick reactions, but of these cases only 2 were definitely confirmed. No patient died, and all the patients reacted well to antitoxin. In this series the proportion of those who had negative Schick reactions in whom diphtheria developed was 0.7 per thousand. SNELLING, Toronto, Canada.

THE EPIDEMIC CURVE OF SMALLPOX. W. J. MARTIN, J. Hyg. **34**:10 (Feb.) 1934.

This is a detailed mathematical study of the curves for epidemics of smallpox occurring in England, Europe and India before and since the use of vaccination. It shows the decline of deaths due to smallpox from 30,000 in England and Wales within from 1837 to 1839 to a total of 113 in London during the past twenty-nine years. The use of vaccination is not the sole factor in the modifying (lessened severity) of the epidemiologic history of smallpox during the past one hundred years. It is not possible to differentiate between the course of the epidemic before and after the introduction of vaccination. Curves depicting the progress and effect of different epidemics are dissimilar, yet are symmetrical and correspond to definite mathematical laws. JANNEY, Wauwatosa, Wis.

TREATMENT OF DIPHTHERIA. J. COMBY, Arch. de méd. d. enf. **37**:65 (Feb.) 1934.

In discussing the management of diphtheria and particularly the thesis recently presented on this subject by Debré, Ramon and Thiroloix, Comby, the dean of French pediatricians, argues for multiple injections of antitoxin at intervals of from twenty-four to forty-eight hours, rather than the single and relatively massive dose recommended by the authors cited. His contention supports the American practice of repeating a moderate dose of the serum if the pseudomembrane persists after the first injection. A number of clinical observations are described in detail.

AMESSE, Denver.

OCULAR MANIFESTATIONS OF MUMPS. H. VILLARD, H. VIALLEFONT and J. TEMPLE, Arch. Soc. d. sc. méd. et biol. de Montpellier **14**:93, 1933.

The eye is rarely involved in mumps. Dacryadenitis, analogous to the parotitis, is most frequent. Other complications reported are conjunctivitis, keratitis, iritis, iridocyclitis, cycloplegia, retrobulbar neuritis and neuroretinitis. The latter generally clears, but may occasionally end in optic atrophy.

With the aid of the binocular ophthalmoscope, mild but definite papilledema was demonstrated in the case described. The spinal fluid with its increased pressure and minimal cellular reaction indicated serous meningitis. The visual acuity was undisturbed. LEBENSOHN. [ARCH. OPHTH.]

ACUTE INTUSSUSCEPTION COMPLICATING PERTUSSIS IN AN INFANT; REDUCTION BY BARIUM SULPHATE ENEMA. M. FERRU, PÉROCHON and LUSSAULT, Bull. Soc. de pediat. de Paris **30**:197 (March 15) 1932.

A boy, 5 months old, showed intussusception of the transverse colon about the fifteenth day after the onset of whooping cough. A barium sulphate enema was given, and the intussusception was easily reduced by this method. The authors believe that a barium sulphate enema administered under the guidance of the fluoroscope has a definite place in the diagnosis and treatment of intussusception. Surgical intervention may thereby be avoided, and when it is indicated by failure or uncertainty after the barium sulphate enema has been tried, the surgeon has a better idea of where the obstruction is located as a result of the preliminary roentgen examination.

BENJAMIN, Montreal, Canada.

EFFICACY OF ANTIDIPHTHERITIC SERUM IN MAN. I. PISU, Pediatria **41**:887 (July 1) 1933.

The author gives a comprehensive review of the literature on the efficacy of antidiphtheritic serum as a definite therapeutic agent in man and discusses his observations and conclusions. His conclusions are summarized as follows:

1. In cases of medium severity, by giving injections of the serum early, during the stage marked solely by local findings, with no evidence of toxemia, it is possible to secure a cure. The rapidity and completeness of the disappearance of the local lesion and its complete repair depend entirely on how early the serum is administered.

2. This action can be explained by the fact that, although the serum is not antibactericidal, it is capable of neutralizing the toxic elements which are liberated from the local lesion, thereby permitting the tissues to exercise their own bactericidal and reparative processes.

3. These clinical facts are, therefore, in perfect accord with the experimental data of d'Antona.

4. It is not possible, on the basis of the author's observations, to deny the curative action of antidiphtheritic serum without giving due attention to the severity of the infection in a given case, as well as to the duration of the disease at the time of the administration of the serum.

SIGNORELLI, New Orleans.

TEN YEARS OF SERUM THERAPY IN SCARLATINA. ERMANNO LIZIER, Pediatria **41**:893 (July 1) 1933.

In this article Lizier reports observations made at the Hospital Santa Maria Maddalena, in Trieste, during a period of ten years and covering more than three thousand cases of scarlatina. The report is a comparative one and covers a complete study of various therapeutic measures.

The author concludes that none of the various methods of therapy produced satisfactory results, except that employing the antiscarlatina serum of Dick, the use of which notably reduced the mortality of scarlatina in this hospital from 10 to 2 per cent. He discusses his observations concerning the hygienic and dietetic management of scarlatina, as well as the complications.

SIGNORELLI, New Orleans.

AURAL COMPLICATIONS IN PERTUSSIS. G. GENOESE, Pediatria **42**:31 (Jan. 1) 1934.

This article represents conclusions based on clinical observations in a great number of cases of whooping cough. The author points out that aural complications, such as earache, otorrhagia and otitis, are frequent. Besides intense pain, these complications may give rise to fever and a feeling of illness or may even produce such alarming phenomena as great restlessness, meningeal reaction

and convulsions. The author strongly suggests that in all cases of whooping cough, especially if associated with hypertrophied adenoids, examination of the ears carried out as a routine by an otologist is essential.

SIGNORELLI, New Orleans.

SUBACUTE MENINGITIS FOLLOWING PERTUSSIS. LUIGI AMITRANO, Pediatria **42**:68 (Jan. 1) 1934.

The author reports a case of subacute meningitis following whooping cough, in which bacteriologic examination of the spinal fluid and necropsy revealed the presence of an organism similar to the Bordet-Gengou organism. The article briefly records the clinical manifestations of nervous complications in whooping cough and reviews several interpretations of the etiology and pathogenesis in these cases.

SIGNORELLI, New Orleans.

NEUROVEGETATIVE SYNDROME IN ACUTE ARTICULAR RHEUMATISM IN INFANTS. C. DEMURTAS and U. SENIN, Pediatria **42**:113 (Feb. 1) 1934.

In fourteen children suffering from acute articular rheumatism the authors studied the effects of the disease on the vegetative nervous system and made comparisons with observations in adults. They found that in children one branch of the vegetative nervous system does not preponderate over the other, but that there are oscillations in the excitability of both branches, and they believe that this fact explains the reason for the inconsistent results observed in studying reactions of the vegetative nervous system in rheumatic children.

SIGNORELLI, New Orleans.

CEREBRAL LESIONS OF DIPHTHERITIC ORIGIN. J. M. DA ROCHA, Arch. de pediat. Rio de Janeiro **7**:613 (March) 1934.

A child, 4 years of age, received two injections of 15,000 units of antitoxin. About one month later, the patellar and achilles reflexes, as well as many of the olecranal reflexes, disappeared. The spinal fluid contained 42 cells per cubic centimeter. The child was greatly prostrated and died a week later. Excellent photographs of the brain are shown. Da Rocha classes this case in the category of hemiplegias of diphtheritic origin, without embolism or thrombosis. This case resembles the cases of Halle, Bloch and Foix, and those of Armand Delille and Vibert.

SANFORD, Chicago.

ANTIDIPHTHERITIC IMMUNIZATION. JUAN L. MORALES GONZALEZ, Pediatría españ. **22**:375 (June) 1933.

The author advocates immunization against diphtheria through the nasal route. From 3 to 5 drops of toxoid (Ramon) are instilled daily into both nostrils over a period of eight days. Eight days later a second course of equal length is given. At times a third is required.

More than 1,000 children were immunized in this manner. Of this number 500 were given the Schick test as a control. The ages of the subjects varied between 8 months and 7 years.

Immunization appeared to be successful in about 96 per cent of the cases.

SCHLUTZ, Chicago.

LECITHIN-DIPHTHERIA ANATOXIN COMPLEX AS ANTIGEN. C. E. PICO and F. MODERN, Rev. Soc. argent. de biol. **9**:427 (Oct.) 1933.

Pico and Modern report the technic and results of experiments they performed to investigate the rôle that lecithin plays in toxic and immunologic phenomena

in diphtheria. The authors say that large doses of lecithin form with diphtheria anatoxin a complex which acts as an antigen for diphtheria toxin. This complex is capable of modifying the reaction of the organism to diphtheria toxin.

POSTVACCINAL DISEASES. W. BLACHER, Jahrb. f. Kinderh. **148**:26 (Feb.) 1934.

The author makes a plea for a more critical analysis of cases of postvaccinal encephalitis and reports two cases. He also reports two cases in which latent tuberculosis apparently was activated by vaccination.

CLAUSEN, Rochester, N. Y.

DIPHTHERIA CARRIERS IN SCHOOL. A. VON ZSINDELY, Arch. f. Ohrenh-, Nasen- u. Kehlkopfh. **137**:215 (Dec. 11) 1933.

Von Zsindely examined cultures from the noses and throats of 1,115 school children for diphtheria bacilli. The percentage of carriers was higher among the boys than among the girls (7 per cent and 5.1 per cent, respectively). Developmental anomalies, such as enlarged tonsils, adenoid vegetation or narrowed nasal passages, appeared to offer favorable mediums for the persistence of bacteria. The presence of carriers with virulent organisms did not invariably lead to an outbreak of diphtheria; conversely, cases of diphtheria developed in the neighborhood of carriers of avirulent organisms. Carriers in schools in all probability transmit the organisms to their neighbors, who may also become carriers.

EDITOR'S ABSTRACT. [ARCH. OTOLARYNG.]

AN EPIDEMIC OF PFEIFFER'S GLANDULAR FEVER. E. SCHULZ, München. med. Wchnschr. **80**:1809 (Nov. 17) 1933.

Glandular fever occurs often in medical students and physicians. The condition is frequently incorrectly diagnosed. Schulz mentions cases in which the condition was considered to be sepsis, aleukemic lymphadenopathy or infection with an atypical lymphocytic reaction. He reports thirty-five cases which he saw from May until July. The incubation period is difficult to determine, but is probably from a few days to a week. At the onset adults usually complain of fatigue and drowsiness, whereas children are irritable and restless. Other prodromal symptoms are anorexia, profuse sweating, headache and abdominal pain. The fever may be septic or simulate that of typhoid fever. After from one to fourteen days (usually two days) the fever drops by lysis. After an afebrile period of from five to twenty-four days there is a recurrence of fever. Entirely afebrile cases occur. Enlargement of the lymph nodes occurs either at the onset of the fever or a few days later. The adenopathy is usually generalized. The spleen is enlarged in the majority of cases, but Schulz has seen enlargement of the liver rarely and then in severe cases only. The blood picture with the pathologic lymphocytes is diagnostic. The total white cell count may be normal or as high as 80,000. At the onset of the disease the blood picture may not be characteristic. The prognosis is favorable. The acute symptoms usually subside within a week or two, but the adenopathy and the abnormal blood cells may remain longer. In the differential diagnosis one must consider influenza, grip, any form of angina, pertussis, lymphogranulomatosis, sepsis, typhoid fever, appendicitis and agranulocytosis. The treatment consists of the administration of amidopyrine for the fever and of sedatives, the use of gargles and the application of poultices of oil or paraffin to the glands. Persons in contact with the patient should gargle with hydrogen dioxide.

BRAHDY, Mount Vernon, N. Y.

EXPERIENCES WITH SERUM FROM VACCINATED PERSONS. P. LINSER, München. med. Wchnschr. **80**:1841 (Nov. 24) 1933.

Linser used the serum of vaccinated donors for passive immunization of patients. For many diseases animal serum either is not available or has not proved beneficial. The human serum with high specific antibody titer was given to patients with

gonococcic sepsis, streptococcic sepsis, gonorrheal epididymitis and infection with Streptococcus viridans. The serum is obtained from the donor from two to four weeks after vaccination with a particular organism. Several hundred cubic centimeters of serum can be given to the patient intravenously, and the more severe the infection the larger the quantity of serum administered. After many years of experience Linser recommends the method highly. It is harmless to both patient and donor and closely simulates the natural method of overcoming infections.

BRAHDY, Mount Vernon, N. Y.

HISTOPATHOLOGIC STUDIES OF ENCEPHALITIS AFTER CHICKENPOX (ENCEPHALITIS POSTVARICELLOSA). L. VAN BOGAERT, Ztschr. f. d. ges. Neurol. u. Psychiat. **140**:201 (June) 1932.

During the course of a severe case of chickenpox in a girl, aged 12, there developed an intense meningeal reaction, followed later by acute ataxia with choreiform movements, pyramidal disturbances and insomnia. There were a bilateral Babinski sign and incontinence. Lumbar puncture revealed an increased pressure, with hyperalbuminosis but no increase in the cell count.

Study of the brain revealed an acute degenerative involvement situated chiefly in the cerebrum and cerebellum, but also in the basal ganglions. There was a diffuse infiltration of the gray masses, in foci at the junction of the gray and white matter and in the white matter of the cerebellum. The areas of demyelinization varied in size from that of a miliary focus to that of a cerebellar leaflet. Often they were situated around vessels, but not so much as in measles and postvaccinal encephalitis. The pallidum was particularly involved, the thalamus less and the caudate nucleus and putamen almost not at all. The frontal and parietal areas were the chief fields affected in the cortex. The Betz and Purkinje cells were particularly involved. The substantia nigra, the gray formations in the pons and medulla and the olivary bodies were intact. The spinal cord showed a slight infiltration around the posterior and anterior roots. The peripheral nerves (sciatic, popliteal, radial and ulnar) were intact. So, too, were the spinal ganglions, the cervical sympathetic and solar plexus ganglions and the gasserian ganglion. Meissner's and Auerbach's plexuses were not examined.

The areas of demyelinization were present chiefly in the centrum ovale (frontal, parietal and temporal), the cerebellum and the inferior cerebellar peduncle. They were not found elsewhere; the cord, in particular, was not involved. The ganglion cells in the cortex were not much involved, except those mentioned. The axis-cylinders were rather markedly involved, even outside the foci of demyelinization. Gliosis, especially by fibrous glia, was marked in the foci.

The picture seems to resemble closely that of multiple sclerosis. It differs from it in the fact that, in contrast, the axis-cylinders are also involved. This has been demonstrated before by others. In addition, the absence of foci in the gray masses is not in keeping with multiple sclerosis. The localization of the lesions in encephalitis following chickenpox is of great significance and is similar to that after vaccination and measles. A similar case reported by Zimmermann and Yannet differs from that of van Bogaert in the absence of perivascular plaques and of inflammation, as well as in the acuity of the lesion.

ALPERS, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

NASAL DIPHTHERIA IN INFANCY. H. STUX and Z. ZIRULNIK, Acta pædiat. **15**:26 (Nov. 6) 1933.

Although pharyngeal diphtheria is uncommon in infants under 1 year of age, the authors encountered diphtherial infection of the nasal passages and skin rather frequently in children of this age period. Among 1,647 infants whom they examined from 1926 to 1930 they failed to encounter a single case of primary faucial or laryngeal diphtheria; during this period they met with 106 cases of extrapharyngeal infection in infants. This figure does not include diphtheria carriers without clinical manifestations. The diagnosis was confirmed bacteriologically in all cases. Of

the 106 patients, 78 were under 8 months old. Sixty per cent of the infants suffered from an antecedent disease which was thought to predispose them to diphtheria.

The clinical course of nasal diphtheria in infants is apt to be subacute or chronic; the disease is usually mild, and the prognosis is good. Membrane formation is uncommon; its absence may render the diagnosis difficult. The most characteristic sign is moderate thickening and hyperemia of the nasal membranes, with moderate mucous secretion and a tendency to bleed. Bacteriologic examination is essential for diagnosis, although antitoxin may be administered before the results of the culture are known. Immunologic reactions may be used to differentiate between true nasal diphtheria and nondiphtherial coryza in a carrier.

The commonest complication of nasal diphtheria is involvement of the skin of contiguous portions of the face. It is alleged that the Klebs-Löffler bacillus may produce complicating bronchopneumonia; otitis media is common.

The outcome of specific therapy is gratifying. The dosage of antitoxin employed varies between 2,000 and 20,000 units; the average therapeutic dose is approximately 4,000 units. Therapeutic results are satisfactory, even when serum is administered late; clinical manifestations usually disappear within two or three days. The presence of organisms in the nasal discharge is not influenced by specific treatment.

Dissemination of the disease is prevented by careful isolation. Marfan advised the local application of a 7.5 per cent solution of neoarsphenamine. Active immunization is of relatively little value in infants under 7 months of age, although it is usually efficacious after this period. Passive immunization is advised during the first six months of life; 3,000 units of antitoxin are used. Immunization so conferred lasts approximately three weeks.

McCUNE, New York.

Chronic Infections

A REPORT ON INSTRUCTION REGARDING SYPHILIS IN AMERICAN MEDICAL SCHOOLS. M. J. EXNER, Am. J. Syph. **17**:449 (Oct.) 1933.

A review is presented of the extent to which syphilis is studied in various medical schools, information having been acquired by questionnaires. The author thinks that there is an improvement in the appreciation of the importance of syphilis, but believes that there should be a special course on syphilis and that an average of at least sixty-eight hours should be devoted specifically to this disease.

ROYSTER, University, Va.

CONGENITAL SYPHILIS: ADVANTAGE OF EARLY TREATMENT AS JUDGED BY THE WASSERMANN TEST. LOUIS CHARGIN and MAURICE UMANSKY, Am. J. Syph. **17**:468 (Oct.) 1933.

The authors first discuss the value of the Wassermann test during the neonatal period and the advisability of carrying out subsequent tests, on both known syphilitic and nonsyphilitic mothers. They recognize that a positive Wassermann reaction in the neonatal period may become negative after two or three months, without treatment, showing in most instances that the child has not acquired the disease. They also point out the fact that a negative Wassermann reaction in the neonatal period may become positive after a few days or a few months, with or without clinical signs of syphilis. The latter fact is difficult to understand.

They then present in statistical form the results obtained at Mount Sinai Hospital, New York, over a period of years in the treatment of syphilitic infants. They lay particular stress on their technic, which is largely that of Fordyce and Rosen. They conclude that the earlier syphilitic treatment is begun after recognition of the disease in infants the sooner cure will be effected. The disappearance of clinical manifestations must not be the only guide; after the disappearance of these manifestations the Wassermann reaction should become negative before treatment is discontinued.

ROYSTER, University, Va.

THE MEANING AND RELIABILITY OF UMBILICAL CORD WASSERMANN TESTS. JOSEPH ROBY and PAUL A. LEMBEKE, Am. J. Syph. **17**:473 (Oct.) 1933.

A statistical and tabulated study of the experience of the authors is reported, together with a brief comment on the reported experience of other investigators. The following conclusions are reached:

1. Wassermann reactions of the umbilical cord reflect almost exactly the condition of the mother's blood at the time of labor. If the reaction of the mother's blood is negative, that of the cord blood will be negative; if the reaction of the mother's blood is positive, that of the cord blood will be equally positive.

2. The substance causing the Wassermann reaction passes out of the child's blood in most cases by the end of two months, leaving the reaction of the blood frankly negative, provided that the child does not have syphilis.

3. If the child has syphilis, the Wassermann reaction of the blood remains as strongly positive after a number of days and weeks as it was for the cord blood.

4. The decreasing Wassermann reaction means that the child does not have syphilis and that treatment should be withheld.

5. If treatment is instituted in new-born children with positive reactions of the cord blood, not too much credit should be given to the drug used.

6. It will be observed that most of these children and many of the mothers have been treated with sulpharsphenamine intravenously. Just as the authors agree with Dunham concerning the Wassermann reactions, so they find themselves in accord with Denham-White, Brahmachari and Maity, authors of an article published in the *Indian Medical Gazette*, February 1933, and abstracted in the June 10, 1933, issue of the *Journal of the American Medical Association*. Their conclusion was: "The drug (sulpharsphenamine) may be regarded as one of the most innocuous at present in use, its lack of toxicity being most marked in comparison with its high efficacy."

ROYSTER, University, Va.

CONGENITAL SYPHILIS FROM BLOOD TRANSFUSION TO THE MOTHER DURING PREGNANCY. G. RICHARDA WILLIAMSON and ROBERT A. STRONG, Am. J. Syph. **17**:484 (Oct.) 1933.

The authors discuss many reported cases of syphilis following blood transfusion and report their own interesting cases.

1. The transmission of congenital syphilis to an unborn baby, which they believe was the result of a transfusion to its mother during pregnancy from a presumably syphilitic donor, is reported.

2. The apparent inadequacy of the precautions taken in many of the cases reported in which syphilis has been transmitted directly from donor to recipient indicates the necessity of greater vigilance.

3. The fact that a donor is a relative should not deter the physician from taking every precaution possible.

ROYSTER, University, Va.

THIRD GENERATION SYPHILIS. WILEY MITCHELL SAMS, Am. J. Syph. **17**:492 (Oct.) 1933.

A probable case of syphilis affecting the third generation is reported, and the transmission of congenital syphilis is discussed.

ROYSTER, University, Va.

ROSENTHAL TEST (MICROPRECIPITATION) IN SYPHILIS AND YAWS. E. C. SMITH and G. L. ELMES, Am. J. Trop. Med. **13**:595 (Nov.) 1933.

The authors describe in detail the preparation of the antigens used in this test. They then describe the technic of the test and briefly discuss its value. They state that the results approximate closely those obtained with the Kahn technic, but no comparative sensitiveness of the two tests is given. The entire test can be completed in less than an hour.

BURPEE, Augusta, Ga.

TUBERCULOUS PERITONITIS. CHARLES T. OLCOTT and DOMENICO PACCIONE, Am. Rev. Tuberc. **28**:27 (July) 1933.

The authors reviewed the records of persons with tuberculosis of the digestive and female reproductive organs among the last 75,000 patients admitted to the public wards of a large New York hospital, covering a period of eighteen years. One hundred and nine proved cases of tuberculous peritonitis were found, 90 of which were clinical cases and 19 of which were cases which came to autopsy. In 18 cases, all of which were clinical, no other lesions were found. The follow-up in 13 of these indicated that 7 patients were living after more than one year, 5 were living after less than a year and 1 had died. The average age of the 11 females with clinically uncomplicated tuberculous peritonitis was 15.2 years, and that of the 7 males was 17.7 years. Of the clincal cases, 73.8 per cent were in females, while the number which came to autopsy was rather higher in males (after allowing for the higher rate of autopsies in the males). The incidence of clinical cases of tuberculous peritonitis in Italians and American-born persons with Italian names was two and one-half times that in the entire number of patients admitted to the hospital. This group largely represented young women.

EUGENE SMITH, Ogden, Utah.

THE VACCINATING PROPERTY OF DISSOCIATED HEAT-KILLED S TUBERCLE BACILLI. W. B. SOPER, L. K. ALPERT and M. J. ADAMS, Am. Rev. Tuberc. **28**:667 (Nov.) 1933.

An investigation was undertaken to determine whether the heat-killed S variant of the bovine tubercle bacillus (dissociated by the method of Petroff) possesses a capacity for immunization in the rabbit greater than that of the heat-killed undissociated bacillus. It was tested against two bacillus vaccines: that of the living human bacillus and B C G. The results of these tests indicated that the animals vaccinated with the heat-killed S tubercle bacilli were the best protected, as judged by both survival and observations at autopsy. The animals vaccinated with living human bacilli and B C G were about equally well protected. The results suggest that the heat-killed S variant possesses greater antigenic properties than does the heat-killed undissociated bacillus and point out possibilities in regard to vaccination which merit further study.

EUGENE SMITH, Ogden, Utah.

FIRST-INFECTION AND REINFECTION TYPES OF TUBERCULOSIS. J. ARTHUR MYERS, Am. Rev. Tuberc. **28**:793 (Dec.) 1933.

The first-infection type of tuberculosis is a benign condition, with lesions which may at any time liberate bacilli into the blood stream or into allergic tissues, resulting in rapidly progressive miliary tuberculosis or chronic disease of the lungs, bones and joints or other parts of the body. The immunity conferred by the first-infection type is not complete. While it may tend to influence the chronicity of the reinfection type, this is of slight value, in view of the fact that the reinfection type cannot develop except on a basis of the first-infection type, and in a certain percentage of cases of the reinfection type the disease results in illness and even fatal termination. One is no longer justified in speaking of tuberculous infection without disease, for these are the same thing. The fact emerges that control of tuberculosis means prevention. A satisfactory immunizing agent is not an actuality; prevention is. Employment of epidemiologic measures holds the same promise for tuberculosis as it does for other communicable diseases.

EUGENE SMITH, Ogden, Utah.

THE SIGNIFICANCE OF TUBERCULOUS LESIONS FOUND IN ADOLESCENT CHILDREN IN A SCHOOL SURVEY. H. W. HETHERINGTON, Am. Rev. Tuberc. **28**:827 (Dec.) 1933.

Reexamination of adolescent school children after an interval of from thirty to forty-eight months confirmed the opinion of the author that apical tuberculous

lesions of slight extent may be controlled by an altered regimen. More extensive lesions that give rise to even trivial symptoms or physical signs are likely to progress, unless treated. Latent nonapical tuberculous infiltration of the lung that appears soft or flocculent in the roentgenogram may result in extensive disease, unless treated. If its appearance is strandlike, it is rarely, if ever, clinically significant. Children with calcification of the tracheobronchial lymph nodes resulting from contact in childhood are not more likely than others to contract apical tuberculosis later, unless the contact is continued or occurs again during adolescence.

EUGENE SMITH, Ogden, Utah.

A STUDY OF THE GROWTH IN AREA OF INTRACUTANEOUS TUBERCULIN REACTIONS. CHESTER A. STEWART, Am. Rev. Tuberc. **28**:844 (Dec.) 1933.

From his study of the details of the growth in area of positive Mantoux reactions following the use of different amounts of tuberculin, Stewart concludes that one can predict with reasonable certainty the average maximum area of intracutaneous reactions, or degree of allergy, in children who have primary tuberculosis exclusively. The area of the cutaneous reaction is not directly proportionate to the amount of tuberculin used. However, the time required for the intracutaneous reaction to attain its maximum area is directly related to the degree of hypersensitiveness, and the relative rapidity with which the area-increment impulse is expended is inversely related to the degree of allergy.

EUGENE SMITH, Ogden, Utah.

THE PASSAGE OF ARSENIC THROUGH THE HUMAN PLACENTA FOLLOWING ARSPHENAMINE THERAPY. N. J. EASTMAN and A. L. DIPPEL, Bull. Johns Hopkins Hosp. **53**:288 (Nov.) 1933.

Neoarsphenamine in doses of 0.3 Gm. and arsphenamine in doses of 0.2 Gm. were given intravenously to seventeen pregnant women at from nine minutes to twenty-five hours before birth of the infant. At the time of birth large quantities of arsenic were found in the maternal circulation, but no arsenic was demonstrated in the fetal blood. In eleven cases in which the mother had been given arsenic during pregnancy the meconium of the new-born infant was examined for arsenic during the first few days of life. Arsenic was found to be present constantly but in variable amounts, and the amount found seemed to bear no relationship to the amount of arsphenamine which the mother had received during pregnancy.

The mechanism by which arsenic (either in the arsphenamine or in the products of its decomposition) reaches the fetus cannot be explained. The authors believe that it does not pass by a process of simple diffusion but that it is transmitted in minute quantities by some other mechanism.

LYTTLE, New York.

TUBERCULOSIS OF BONES AND JOINTS. FRANK D. DICKSON, J. Missouri M. A. **31**:63 (Feb.) 1934.

The author emphasizes the importance of an early diagnosis in this condition. Roentgen rays, while often of greatest value, cannot always be relied on for early diagnosis. Biopsy should seldom be performed, unless one is prepared to follow this with a fusion operation, lest a sinus be formed.

Tuberculosis is a generalized disease, so in these cases treatment should be general as well as local.

In case of doubt, a provisional diagnosis of tuberculosis should be made, and treatment should be instituted accordingly. If the diagnosis must be revised later, no harm has been done, and the safest course has been followed.

There are two end-results in tuberculous disease of the joints; free motion or bony ankylosis. The former outcome can be secured in a certain percentage of cases of synovial tuberculosis in children by conservative treatment; the latter can be secured only by adequate fusion operation.

BERGER, Kansas City, Mo.

CONGENITAL SYPHILIS. R. P. SCHOWALTER, Wisconsin M. J. **33**:39 (Jan.) 1934.

The incidence of congenital syphilis in the Milwaukee County Home for Dependent Children was 2 per cent for the 565 children present. The incidence for a ten year period in 6,193 children was 0.56 per cent. Most cases were not detectable by physical examination alone. Typical stigmas were rare. Three syphilitic infants died of bronchopneumonia; three were feebleminded. In 9 of the 13 who remained in the home long enough to have treatment for more than one year, the Wassermann reaction became negative and remained so. Early treatment produced good results, but when treatment was begun after the fifth year it was difficult to get a persistently negative Wassermann reaction.

Mercury ointment rubs and sulpharsphenamine have been chiefly used during the past five years.

JANNEY, Wauwatosa, Wis.

HUMAN TUBERCULOSIS OF BOVINE ORIGIN. WILLIAM G. SAVAGE, Brit. M. J. **2**:905 (Nov. 18) 1933.

The author discusses the relative incidence of tuberculosis in man due to the human and the bovine type of bacillus, giving statistical tables indicating the parts of the body most frequently affected. He discusses the path of entry, the virulence of the two strains and the possibility of adaptation and growth mutation and then places statistically bovine infection in man at a high figure in England. Over 40 per cent, and possibly in some instances more, of all the cattle in England are infected with tuberculosis. A sharp line, however, is drawn between tuberculin reactors and those conveying living bacilli in the milk.

He recommends segregation of the cattle, the simple reactors to be placed in the segregated area and their calves to be fed only heated milk. In this way he thinks perhaps the large amount of bovine tuberculosis in cattle can be eliminated. The chronically and actively infected cattle should be destroyed, and compensation should be made by the Government to the extent of not the full value of a healthy cow but that of an injured cow, which is about two-thirds the value of a normal healthy cow. In this way he hopes that eventually tuberculosis of the bovine type in cattle may be eliminated. In the meantime, universal pasteurization of milk should be practiced.

ROYSTER, University, Va.

ARTIFICIAL PNEUMOTHORAX IN THREE CASES OF PULMONARY TUBERCULOSIS IN CHILDREN. WILLIAM STOBIE, Brit. M. J. **1**:14 (Jan. 6) 1934.

The author reports three cases of pulmonary tuberculosis: (1) in a girl, aged 9 years, (2) in a boy, aged 12 years, and (3) in a girl, aged 15 years, in which the patients were treated by artificial pneumothorax, with favorable results.

ROYSTER, University, Va.

BLOOD CULTURE IN TUBERCULOSIS. W. J. PENFOLD and H. M. BUTLER, M. J. Australia **2**:837 (Dec. 23) 1933.

The authors review the various reports on the isolation of tubercle bacilli from the blood of tuberculous patients and record their own experience in this connection. Using the Löwenstein method of blood culture, they were able to cultivate Bacillus tuberculosis in only three of twenty cases. Because positive results were so few and because the method is so troublesome and time-consuming, they believe that it is of little value in the clinical diagnosis of tuberculosis.

GONCE, Madison, Wis.

AMYLOID DISEASE IN A PATIENT WITH BONE TUBERCULOSIS, UNCOMPLICATED BY SECONDARY INFECTION; TREATED WITH LIVER EXTRACT. H. J. SEDDON, Proc. Roy. Soc. Med. **27**:124 (Dec.) 1933.

A boy, aged 10 years, was admitted to the hospital with tuberculosis of the right foot and left elbow. The elbow healed under treatment; the foot

became worse, and finally amputation through the upper middle third of the tibia was performed. Two years later, tuberculosis of the spine and right ilium developed. Six months later, amyloid disease appeared, with the typical enlargement of the liver and spleen and albuminuria. There was no sign of secondary infection. Sections obtained by puncture of the liver showed advanced amyloid disease. Liver extract equivalent to 1 pound (453.5 Gm.) of fresh liver was given daily for six months. With this treatment the patient improved remarkably.

WILLIAMSON, New Orleans.

MILIARY TUBERCULOSIS IN INFANTS. P. ARMAND-DELILLE and H. GAVOIS, Paris méd. **1**:17 (Jan. 6) 1934.

The authors state that the so-called miliary granule seen in the lung in tuberculosis shows several stages. It is indicative of a primary infection. Its next course may be a generalized miliary form causing death, with or without meningeal irritation. However, instead of this it may become a "cold granule" (this applies to a miliary form without changes in temperature), or it may be carried along the blood stream to the serous membranes, such as the pleura and peritoneum, or to osseous tissue.

SANFORD, Chicago.

CONGENITAL TUBERCULOSIS. LUIGI AURICCHIO, Pediatria **41**:841 (July 1) 1933.

The author reports his observations in the Royal Pediatric Clinic of Naples on ten infants born of tuberculous mothers. The disease in the mothers was advanced and active to such an extent that six of the mothers died of it shortly after the infants' birth.

The infants were removed from contact with the mothers immediately after birth and were supervised closely for periods of from one to four years. At no time did any of these infants manifest positive evidence of tuberculous infection, either clinically, roentgenologically or by tuberculin tests, thus establishing the conclusion that, at least in these cases, tuberculous infection did not exist as a congenital infection.

These positive exclusions, in cases in which the mothers were afflicted with advanced and active tuberculosis, appear to confirm the opinion that tuberculosis is transmitted by contact.

SIGNORELLI, New Orleans.

VARIATIONS OF THE CALCIUM AND POTASSIUM CONTENT IN THE BLOOD SERUM DURING INOCULATION WITH TUBERCULIN. GUISEPPE MELODIA, Pediatria **41**:1506 (Dec.) 1933.

In a study concerning the calcium and potassium content of the blood serum during the period of inoculation with tuberculin in children known to be afflicted with tuberculosis, the author observed a diminution of the potassium content and an increase of the calcium content. In a control experiment, he carried out the same studies on normal children and found that the calcium content exhibited no modification, while the potassium content showed a slight diminution, which, however, never reached the point observed in tuberculous children.

SIGNORELLI, New Orleans.

DIABETES INSIPIDUS IN A SYPHILITIC CHILD. V. CATINI, Prat. pediat. **11**:275 (Aug.) 1933.

This is the report of the case of a 5 year old girl who had had enuresis since the age of 2 and in whom extremely severe polyuria and polydipsia had gradually developed. Her mother had had three abortions and was delivered of a macerated fetus before the conception of this child. On examination the patient was found to have a mass in the right sternoclavicular region which a roentgenogram showed to be an osteoperiostitic process. The Wassermann reaction of the blood was 4 +.

She excreted from 5 to 6 liters of urine daily. The specific gravity of the urine was 1.002; examination of the urine showed no albumin or sugar; 1.2 per cent chlorides, and 7.2 Gm. of sodium chloride within twenty-four hours. After thirty mercurial inunctions the tumor disappeared and both the thirst and the polyuria diminished.

DOOLEY, Kent, Conn.

THE HEMORRHAGIC DIATHESIS AND TUBERCULOUS INFECTION. F. DE LUCA, Prat. pediat. **11**:366 (Nov.) 1933.

The author reviews the literature with regard to the association between tuberculosis and the hemorrhagic diathesis and reports two cases of purpura in children with tuberculosis.

DOOLEY, Kent, Conn.

THE PIRQUET REACTION IN CHILDREN. H. B. DE MACEDO, Arch. de pediat., Rio de Janeiro **5**:399 (Sept.) 1933.

The author tested 433 school children from 6 to 14 years of age with the Pirquet test. The reaction was positive in 27.7 per cent. Of these, 271 were boys, 25.5 per cent of whom gave a positive reaction, and 162 girls, 29.6 per cent of whom gave a positive reaction. The age group ran from 6 to 8 years, 21 per cent; from 9 to 11 years, 31 per cent, and from 12 to 14 years, 33 per cent.

SANFORD, Chicago.

TUBERCULOSIS TREATED BY PNEUMOTHORAX. A. L. STOCKLER and E. FILGUEIRAS, Arch. de pediat., Rio de Janeiro **5**:407 (Sept.) 1933.

In a child, at 21 months of age, a roentgenogram showed diffuse tuberculous infiltration of the lobes. During the following year forty-three insufflations of air, varying from 125 to 150 cc. were given. Four roentgenograms taken at various times during this period showed improvement. The last showed that the lungs were remarkably clear.

SANFORD, Chicago.

PSEUDOPARALYSIS OF PARROT. C. R. CASTILLA and O. J. MONTANARO, Rev. med., Buenos Aires **19**:112 (Nov.) 1933.

A case of Parrot's pseudoparalysis in an infant is described, with accompanying photographs and roentgenograms of the epiphysis. This condition must be differentiated from obstetric paralysis, paralysis of central origin and atrophic paralysis.

SANFORD, Chicago.

DEMONSTRATION OF TUBERCLE BACILLI IN THE BLOOD OF CHILDREN. KARL RUPILIUS, Arch. f. Kinderh. **101**:48 (Dec. 19) 1933.

Blood cultures for tubercle bacilli according to the Löwenstein technic were done on 96 children, most of whom were known to have active or latent tuberculosis. There were only three positive cultures, one from an infant with far-advanced pulmonary tuberculosis with cavitation, one from a boy with active rheumatic arthritis who had given a positive reaction to tuberculin and one from a girl with active chorea. The author was much more successful in demonstrating tubercle bacilli in this series of children by other means, such as examination of the sputum and the stomach washings and inoculation of guinea-pigs. No positive results were seen when blood from the children was injected into guinea-pigs. Whereas Löwenstein reported more than 50 per cent positive blood cultures in a series of 408 cases, other authors, in repeating his work, obtained only 6.2 per cent positive cultures in 1,312 cases. No explanation for this discrepancy is offered. Without doubt, some patients with tuberculosis have bacillemia. The presence of tuberculosis in children with arthritis and chorea who show negative tuberculin reactions was not confirmed.

LEMASTER, Evanston, Ill.

THE DIAGNOSIS OF SYPHILIS FROM A DRIED DROP OF BLOOD. PETER DAHR, Deutsche med. Wchnschr. **60**:94 (Jan. 19) 1934.

This method was described by Cheviack in 1932. The technic is as follows: A drop of blood is placed on a slide, defibrinated by shaking and dried. Three and five-tenths per cent sodium chloride and 0.03 per cent sodium hydroxide are used to hemolyze this. Three hundredths cubic centimeter of a 1:10 dilution of the Meinicke antigen is also needed. The dilution is made with the salt solution just mentioned. The mixture is then placed in a paraffin ring on another slide and allowed to stand for ten minutes in a wet chamber at 56 C. Shaking for three minutes is the next step. After the mixture has remained for half an hour in a moist environment at room temperature, the reaction is read. In case of a negative reaction, brownish sandlike particles are seen. In case of a positive reaction, red-brown floccules are visible.

Dahr used this method in six hundred cases and compared the reaction with the Kahn, Meinicke and Wassermann reactions. He found that the Cheviak method gave results identical with those mentioned, more elaborate reactions being obtained in 91 per cent of the cases. Pregnancy, cancer, tuberculosis, full stomach, etc., do not give false positive reactions with the Cheviak method, whereas in such conditions the Wassermann reaction may become misleadingly positive. The Cheviak method (1) is simple, requiring only a drop of blood; (2) can be carried out several days after the blood is taken, and (3) gives fewer false positive reactions than other serologic tests. It is especially useful for children and fat persons, in whom it is hard to do venipuncture. Because the reaction can be read a few days after the blood is taken, this method is practical for doctors practicing in isolated localities.

KERESZTURI, New York.

PERIOSTEAL BONE FORMATION AT THE EPIPHYSEAL LINE IN A CASE OF CONGENITAL SYPHILIS. G. GERSTEL, Virchows Arch. f. path. Anat. **289**:516, 1933.

Roentgenologic and anatomic examination of the lower end of each femur of a child who died at the age of 7 weeks of congenital syphilis revealed the presence of osseous outgrowths at the epiphyseal line. The bony masses had been formed by and within the thickened periosteum. The unusual lesion is interpreted as a regenerative reactive process evoked by the destructive osteochondritis that was present at the junction of the diaphysis and epiphysis. Spirochetes could not be demonstrated in the tissues; the patient had been under antisyphilitic treatment before death.

O. T. SCHULTZ. [ARCH. PATH.]

OPEN PULMONARY TUBERCULOSIS AND TREATMENT WITH PNEUMOTHORAX IN OLDER CHILDREN. G. J. HUËT, Maandschr. v. kindergeneesk. **2**:191 (Feb.) 1933.

The author, director of the Amsterdam Sanatorium for Children, Hoog-Blaricum, gives a survey of the pneumothorax treatment in 134 cases of severe open tuberculosis in children, most of whom were from 11 to 15 years old. He comes to the following conclusions:

In highly active forms (those with fever, toxic symptoms and a bad general condition) the pneumothorax treatment is not applicable. Less active forms in which the process does not adjoin the hilus of the lung can be treated in this way, and the condition can be greatly improved, even when the collapse is incomplete. In cases in which the process is situated adjoining the hilus and in which no large cavity exists, it is more advisable, as a rule, to wait and see whether a simple rest cure may restore the patient to health.

As for the large group of borderline cases of moderate activity, the author proposes, when the opportunity for spontaneous recovery seems slight, that pneumothorax be attempted, but that this be discontinued as soon as it appears that a sufficient collapse cannot be obtained.

Cases in which there is a so-called primary focus belong to a separate group. A necrotic primary focus in children is an absolute indication for pneumothorax treatment. The author is of the opinion that patients with a primary focus and analogous processes which show a strong or increasing activity should also be treated in this way, even before the sputum shows a positive reaction.

VAN CREVELD, AMSTERDAM, THE NETHERLANDS.

HERNIA DIAPHRAGMATICA AND PULMONARY TUBERCULOSIS. J. H. G. CARSTENS, Maandschr. v. kindergeneesk. **2**:540 (Aug.) 1933.

A diagnosis of pulmonary tuberculosis associated with diaphragmatic hernia was made in a girl of 2½ years. The diaphragmatic hernia had caused hemorrhages from the stomach and the intestine.

VAN CREVELD, Amsterdam, The Netherlands.

Internal Diseases

THE CLINICAL SIGNIFICANCE OF LEUCOPENIA WITH SPECIAL REFERENCE TO IDIOPATHIC NEUTROPENIA. STACY R. METTIER and HARVEY T. OLSON, Ann. Int. Med. **6**:855 (Jan.) 1933.

A study was made of the hospital records of 10,000 patients. Of this number 1,167 had leukopenia, on the basis of a count of 5,000 leukocytes per cubic millimeter as representing the low standard for normal.

A table giving the various conditions in which leukopenia occurred is presented. Fifty-two and four-tenths per cent of the total number of cases of leukopenia occurred in females and 47.6 per cent in males. The authors divide their cases into two clinical groups: (1) malignant leukopenia of obscure origin and (2) benign leukopenia of obscure origin. Five cases are reported to illustrate these groups, one of which was that of a girl, aged 4 years.

Attention is called to the various reactions of the bone marrow occurring in the cases reported, namely, aplasia of the bone marrow, depression of leukopoiesis only, hyperplasia of the leukopoietic tissue and hyperplasia of the erythropoietic tissue.

READING, Galveston, Texas.

SOME OBSERVATIONS CONCERNING A POSSIBLE INSULIN-INHIBITING SUBSTANCE IN URINE. E. M. WATSON and W. S. DICK, Ann. Int. Med. **6**:1171 (March) 1933.

Stimulated by the work of Karelitz, Cohen and Leader, who demonstrated that the blood of diabetic persons, and, to a lesser extent, that of normal persons, apparently possess something which is antagonistic in its reaction to insulin, Watson and Dick are of the opinion that a similar investigation of the urine would be of interest in this connection. They were able to demonstrate an insulin-inhibiting factor in the urine of both diabetic and nondiabetic persons. Because this substance is destroyed by heating the urine to 60 C. for several hours or by boiling the urine for a few minutes, in all probability it is enzyme-like in character.

READING, Galveston, Texas.

CLINICAL SIGNIFICANCE OF THE SYSTOLIC MURMUR; A STUDY OF 1000 CONSECUTIVE "NON-CARDIAC" CASES. A. R. FREEMAN and SAMUEL A. LEVINE, Ann. Int. Med. **6**:1371 (May) 1933.

Included in this study of 1,000 cases were those of 70 infants and children. The murmurs were graded as to intensity, from grade 1 to grade 6. The authors advise that caution be exercised in attributing no significance to systolic murmurs. While they are frequently present in the absence of heart disease, a proper interpretation of the intensity of the murmur and a proper regard for the causative factors considered in the discussion will aid in more accurate diagnosis, prognosis and treatment of disease.

READING, Galveston, Texas.

ORTHOSTATIC ALBUMINURIA: A COMPARISON WITH OTHER TYPES OF ALBUMINURIA. EDWARD G. THORPE and E. G. WAKEFIELD, Ann. Int. Med. **6**:1565 (June) 1933.

A careful study of 185 patients seen at the Mayo Clinic over a period of ten years is reported. The cases are divided into four groups: (1) orthostatic albuminuria, (2) albuminuria with orthostatic response, (3) latent glomerulonephritis and (4) chronic glomerulonephritis.

One hundred patients with orthostatic albuminuria were studied, 26 per cent of whom were 12 years of age or younger. Lordosis was present in 21 and absent in 11. In the remaining 78 nothing was recorded concerning lordosis.

The authors insist on the following points before a diagnosis of albuminuria is made: (1) absence of even traces of albumin in the urine excreted with the patient in a recumbent position; (2) absence of persistent erythrocytes, casts or more than an occasional erythrocyte or cast in the sediment; (3) absence of a history or physical signs of nephritis, nephrosis or associated vascular changes; (4) normal renal function, as measured by the usual tests, and (5) observation of the patient over a period of several months.

A correct diagnosis of orthostatic albuminuria carries with it a prognosis of good health and longevity in 99 per cent of cases and a probability that in 33 per cent the urine will become free from albumin.

Foci of infection play no part in the production of orthostatic albuminuria. From data presented regarding the etiology of orthostatic albuminuria the authors believe that the burden of proof rests with those who do not consider it due to renal injury.

READING, Galveston, Texas.

THE INCIDENCE AND SIGNIFICANCE OF THE SICKLE CELL TRAIT. L. W. DIGGS, C. F. AHMAN and J. BIBB, Ann. Int. Med. **7**:769 (Dec.) 1933.

Moist preparations were used in these studies. The authors conclude that the sickle cell trait is of little clinical importance. The following observations are found in the summary: 1. The trait is compatible with long life. 2. The incidence in patients in hospitals has not proved to be higher than that in healthy persons. 3. Ulcers of the leg and greenish discoloration of the sclera appear as frequently in persons without the trait as in those with the trait. 4. Hemoglobin determinations in a series of Negro school children revealed parallel findings in those with and without the trait. 5. The ratio of sickle cell anemia to the sickle cell trait is estimated as 1:40. 6. The importance of the sickle cell trait appears to be limited to the relatively small group of persons who, in addition to the trait, have sickle cell anemia.

READING, Galveston, Texas.

FRAGILITAS OSSIUM IN FIVE GENERATIONS. HENRY JOACHIM and MILTON G. WASCH, Ann. Int. Med. **7**:852 (Jan.) 1934.

The authors saw eight cases of fragilitas ossium in one family, covering three generations, and were able to trace the disease in five generations. Three cases are reported, two of which occurred in children aged 9½ years and 13 years, respectively. In addition to characteristic roentgenograms of the bones, a distinct prominence of the veins, indicating sclerosis, was noted in the three cases. The thinning of the shafts of the metatarsal and metacarpal bones, with relative enlargement of the head and base, gave rise to the "dumb-bell" type of bones. The study of the serum calcium was not conclusive in these cases. The condition was associated with blue sclera.

READING, Galveston, Texas.

MYELOID INSUFFICIENCY. R. GOTTLIEB, Ann. Int. Med. **7**:895 (Jan.) 1934.

As a result of myeloid exhaustion there are few, if any, signs of regeneration in this condition. Thrombocytopenia, granulocytosis and anemia are present. In some instances the cause of the condition is arsenic or benzene poisoning; in other

cases the etiology is obscure. Such terms as aplastic anemia, myelophthisic anemia and aleukia haemorrhagica are not expressive of the insufficiency of the myeloid system and should not be used in this connection. A part or the entire myeloid system may be involved. Thus, in agranulocytosis only the granulopoietic apparatus is altered. A number of cases of agranulocytosis eventually show a complete picture of myeloid insufficiency.

The normal inhibitory effect of the reticulo-endothelial system on the myeloid system is discussed, and the theory is advanced that a stimulated and proliferated endothelial system may increase its physiologic inhibition to a pathologic degree. If such a pathologic inhibition persists after the original cause has been removed, it is only logical that complete atrophy of the myeloid system may result.

The case of a 19 year old boy is reported in whom the clinical picture was that of an exhausted myeloid system. There was a reduction in all myeloid elements, giving rise to anemia, granulocytosis and thrombocytopenia. Signs of regeneration, though not entirely absent, were slight. The epinephrine test showed a myeloid response within twenty minutes, which resulted in an increase of white blood cells from 1,900 to 7,800, with a return to the original level within one hour. On the basis of the possibility that the reticulo-endothelial system was the inhibitory factor in this case, the spleen was removed. Following the operation, improvement was marked and rapid. Hypergenerative response was noted in the blood. Improvement, however, was temporary, and death resulted. In spite of the fatal termination, the author is of the opinion that early splenectomy is a means of combating the disease before a completely fatty change has occurred in the myeloid system, as was present in this case. The importance of the epinephrine test and the lack of infection are stressed.

READING, Galveston, Texas.

HYPOGLYCEMIA AND HYPERINSULINISM. MILO K. TEDSTROM, Ann. Int. Med. **7**:1013 (Feb.) 1934.

The mechanism which maintains a normal blood sugar level is discussed. The internal secretions of the ovaries, testes and parathyroids, acting with insulin, reduce the blood sugar, while the secretions of the pituitary, thyroid and suprarenal glands tend to raise the blood sugar level. The article deals only with so-called hyperinsulinism. Symptoms due to hyperinsulinism are described, and it is pointed out that convulsions associated with hypoglycemia closely resemble true epileptic seizures, so that care should be exercised in making a diagnosis of epilepsy unless blood sugar values have been obtained.

READING, Galveston, Texas.

PICK'S DISEASE. ELK TANNENBAUM, Arch. Pediat. **50**:464 (July) 1933.

A case of Pick's disease is reported.

WADDELL JR., University, Va.

A CASE OF GONOCOCCAL ENDOCARDITIS WITH RUPTURE OF THE AORTIC VALVE AND DEATH. WILLIAM B. PORTER, Heart **16**:201, 1933.

A case of gonococcic endocarditis is reported in which rupture of the aortic cusp was heard to take place during life. The rupture was followed immediately by acute and fatal edema of the lungs. A Negress, aged 16, entered the hospital with acute gonococcic vaginitis of four weeks' duration and acute arthritis of two days' duration. The heart showed no demonstrable enlargement. A soft systolic murmur was heard over the precordium. The pulse rate was 118 and regular. The blood pressure was 120 systolic and 65 diastolic. Three days after admission acute gonococcic conjunctivitis developed in the left eye. Nine days after admission the systolic murmur had definitely increased over the base of the heart, and a low-pitched diastolic murmur was audible along the left border of the sternum. A blood culture showed a growth of gonococci. Seventeen days after admission, while the heart was being auscultated, the diastolic murmur suddenly increased in intensity and became musical. The patient soon became dyspneic. Moist râles were heard over both lungs, and pink, frothy fluid began to flow from the nose and mouth,

The pulmonary edema progressed rapidly. The pulse rate rose to 140. The patient became unconscious and died about twenty minutes after the onset of the pulmonary symptoms. Autopsy, performed the following day, revealed edema and congestion of the lungs. The right lung weighed 590 Gm., and the left, 600 Gm. There was a thin, blood-tinged fluid in the bronchi, and the myocardium was soft and pale. The heart weighed 310 Gm. There was perforation of the two anterior aortic cusps, one perforation being 6 mm. and the other 4 mm. in diameter. A low verrucous, friable, pinkish-white vegetation was seen on the margins of the perforations. Microscopically, there were: edema, fibrinous exudation, leukocytic infiltration and moderate histiocytic proliferation in the cusps of the aortic valve, a small abscess in one cusp, scattered foci of interstitial polymorphonuclear infiltration in the myocardium, pulmonary alveoli filled with serous fluid in which were alveolar phagocytes containing blood pigment, and pulmonary congestion. Porter concludes that the change in the diastolic murmur was due to rupture of the aortic cusps, resulting in aortic regurgitation, cardiac failure and pulmonary edema.

ESTHER MARTING. [ARCH. PATH.]

CONGENITAL STENOSIS OF THE PYLORUS. C. E. TRIBBLE, J. A. M. A. **101**:278 (July 22) 1933.

Tribble reports the occurrence of pyloric stenosis in the first and the third child of one family.

BONAR, Salt Lake City.

MYELOPHTHISIS. HARRY M. GREENWALD, J. Pediat. **3**:117 (July) 1933.

Agranulocytosis, aplastic anemia and thrombocytopenic purpura have many similar characteristics in their clinical course and blood pictures and in the changes in the bone marrow. It is not unlikely that each disease is due to congenital inferiority of the bone marrow and that an infection or toxic substance which in a normal person would produce only mild or temporary changes is sufficient to cause severe and widespread disturbance. Changes in the bone marrow are present in these three diseases, and deficient production of one or all of the elements of the blood is encountered. Whether these three conditions are distinct and separate diseases or whether they are closely related and are possibly variants from a common origin cannot be settled at the present time. The author prefers the term panmyelophthisis to aplastic anemia, granulophthisis to agranulocytosis and thrombophthisis to thrombocytopenic purpura. Theories concerning the etiology of these diseases are discussed.

LEMASTER, Evanston, Ill.

FAMILIAL RETARDATION IN OSSIFICATION OF THE CARPAL CENTERS. ARTHUR F. HESS and HAROLD ABRAMSON, J. Pediat. **3**:158 (July) 1933.

In a boy, aged 8 years, only two centers of ossification were present in the wrist. The values for blood calcium and phosphorus were normal. During the ninth year there was a rapid appearance of several centers of ossification. A brother, at 5 years of age, showed only three carpal centers, which gradually increased in number to normal within the following two years. It is assumed that the retardation in ossification of the carpal centers in these two brothers was due to the lack of a local calcifying factor, a mordant or *Kalkfaenger*.

LEMASTER, Evanston, Ill.

PATHOGENESIS OF RENAL RICKETS. A. GRAEME MITCHELL and GEORGE M. GUEST, J. Pediat. **3**:192 (July) 1933.

The results of metabolic studies by various investigators on the excretion of calcium and phosphorus in chronic nephritis in children are discussed. Evidence indicates that in renal insufficiency phosphates are excreted in large amounts through the bowel and can interfere with the absorption of calcium by the forma-

tion of calcium phosphate, which is excreted in the stools. The authors favor the view that this mechanism is principally responsible for the low content of blood calcium and the osteoporosis seen in renal rickets.

LEMASTER, Evanston, Ill.

CHOLESTEROL PARTITIONS OF THE BLOOD IN MYXEDEMA (CRETINISM). HERMAN SCHWARZ and ANNE TOPPER, J. Pediat. **3**:242 (July) 1933.

In a cretin, aged 12 years, the blood cholesterol was high and the basal metabolic rate low, but when medication with thyroid extract was given the value for cholesterol gradually dropped, while the basal metabolic rate rose to normal. The inverse relationship between the total cholesterol level and the basal metabolic rate was again observed after the thyroid extract was discontinued. In children with nephrosis no correlation between the blood cholesterol and the basal metabolic rate could be observed. In one patient with subacute yellow atrophy of the liver the cholesterol ester of the blood was greatly reduced, while the free cholesterol was only slightly diminished, as was previously reported by Thannhauser and by Epstein. The normal ratio between cholesterol ester and free cholesterol was reversed in seven of eleven cases of myxedema in children.

LEMASTER, Evanston, Ill.

ANAEMIAS OF INFANCY AND CHILDHOOD: I. INTRODUCTION. LEONARD G. PARSONS, Arch. Dis. Childhood **8**:85 (April) 1933.

The erythron (reticulo-endothelium of the marrow and extramedullary centers, megaloblasts, normoblasts, reticulocytes and erythrocytes) is more widely spread in infancy than in the adult. There is very little reserve space for bone marrow in the infant. In times of stress the extramedullary centers in the liver, spleen, pancreas and other organs may be recalled into activity. Certain factors (iron, copper, vitamin C and thyroxine) are necessary for the maturation of the normoblast to the erythrocyte. In disease of the erythron there may be hyperplasia, hypoplasia or aplasia. In hyperplasia nucleated red blood cells appear in the circulation, but these cells may not mature. Reticulocytes in the blood stream, however, are a true indication of new formation of blood. A clinical study of the anemias of infancy shows that the majority may be classified in two main groups: (1) those in which there is a deficiency in one or more of the elements necessary for the synthesis of hemoglobin or for the production of the erythrocyte or for both of these (the deficiency or anhematopoietic anemias) and (2) those in which there is increased destruction of the erythronic elements (the hemolytic or erythronoclastic anemias).

KELLY, Milwaukee.

ANAEMIAS OF INFANCY AND CHILDHOOD: II. THE EFFECT OF YEAST ON NUTRITIONAL ANAEMIA IN RATS. LEONARD G. PARSONS and E. M. HICKMANS, Arch. Dis. Childhood **8**:95 (April) 1933.

In experiments on rats it was found that yeast had a curative effect in nutritional anemia and allowed reproduction to occur. The progeny, however, were anemic. The addition of iron to the diet of yeast and milk allowed reproduction to occur and caused the offspring to show hemoglobin greater than normal.

KELLY, Milwaukee.

ANAEMIAS OF INFANCY AND CHILDHOOD: III. THE ANHAEMATOPOIETIC ANAEMIAS (DEFICIENCY DISEASES OF THE ERYTHRON); NUTRITIONAL ANAEMIAS OF PREMATURITY, SCURVY AND COELIAC DISEASE. L. G. PARSONS and J. C. HAWKSLEY, Arch. Dis. Childhood **8**:117 (April) 1933.

Nutritional anemia of a mild degree is almost universal in both breast-fed and artificially fed babies. At times the anemia may become severe. It occurs more frequently in babies, small at birth, who grow rapidly. The condition is due to

a deficiency of iron and can be cured by adding medicinal iron to the diet. The beneficial effect is diminished in the presence of infection. In congenital nutritional anemia there are pallor from birth, hypochromic anemia and absence of marrow response. Hemolysis is excluded by the absence of icterus. Iron therapy in nutritional anemia causes reticulocytosis and a rise in red cells and hemoglobin. The authors are of the opinion that there is enough copper contaminating the iron to give results without the addition of copper, and that copper is necessary for the synthesis of hemoglobin. Anemia is frequent in scurvy. The giving of iron alone has no effect, but if vitamin C is added, reticulocytosis takes place and there is a rise in red cells and hemoglobin.

KELLY, Milwaukee.

COPPER IN THE TREATMENT OF NUTRITIONAL ANAEMIA IN INFANCY. H. M. M. MACKAY, Arch. Dis. Childhood **8**:145 (April) 1933.

Copper is not present in hemoglobin. Iron given to young rats was absorbed and stored in the liver. On receiving copper the iron was used for the synthesis of hemoglobin. In nutritional anemia of children the copper content of the blood was twice the amount in the children used as a control, suggesting: (1) that there was no shortage of copper in the cases of anemia; (2) that the body's need for hemoglobin calls copper into the circulation. Mackay divided the children with nutritional anemia into three groups. One group received from 4½ to 9 grains (0.29 to 0.58 Gm.) of iron and ammonium citrates a day. The second group received these in the same doses and in addition 1/20 grain (0.003 Gm.) of copper sulphate. The third group received from 4½ to 9 grains of saccharated ferrous carbonate daily. Good results were obtained in the three groups, there being no advantage in any group. It seems that there was no deficiency of copper in these cases, and that, while deficiency of copper may occur, it is uncommon.

KELLY, Milwaukee.

INTERPRETATION OF RENAL CHANGES IN LIPOID NEPHROSIS. P. GÉRARD and R. CORDIER, Arch. internat. de méd. expér. **8**:225, 1933.

Gérard and Cordier injected normal serum and serum rich in cholesterol intraperitoneally in a series of salamanders and frogs under varying conditions. Then the kidneys were fixed in solution of formaldehyde, and frozen sections were made and examined with Nicol prisms under polarized light. They found that cholesterol cannot filter through normal glomerular epithelium. However, if this is rendered permeable by previous injection of egg albumin, cholesterol comes through and is deposited in the epithelium of the convoluted tubules. In clinical lipoid nephrosis the albuminuria renders the glomerular epithelium permeable to cholesterol, which thus enters the convoluted tubules and is there reabsorbed by the epithelium.

JACOB KLEIN. [ARCH. PATH.]

JUVENILE OSTEOCHONDRITIS. VAN DE MAELE, J. de radiol, et d'électrol. **17**:317 (June) 1933.

Juvenile osteochondritis consists in noninflammatory disturbances of growth in various centers of ossification at the epoch of their greatest developmental activity, and it is this epoch which determines relatively their appearance, for bone cells are physiologically weak during rapid growth. Endochondral ossification comprises three phases: (1) growth of cartilaginous structure, (2) ossification and (3) secondary haversian ossification, the latter signifying a substitution of secondary compact bone for the primary soft bone. Whenever the balance between resorption and decalcification is disturbed some decided alteration must have occurred to account for it. Ossification takes place in the fetus and in early infancy. The histologic succession in the juxta-epiphyseal region is as follows: first, hyaline and striated cartilage, then a layer of more translucent cartilage, which is bluish and hypertrophied and dilated by imbibition; beneath this a thin layer of hypertrophic calcified cartilage, then the primary zone of endochondral ossification, with

its outer layer of red marrow penetrated by blood vessels; below this the area of resorption of primary endochondral bone and, finally, defined patches of old spongy bone. The various osteochondritic localizations are given as (1) the tarsal scaphoid bone, (2) the sesamoid bones, (3) the apophyses, (4) the epiphyses, (5) the vertebrae and (6) certain less frequent situations. Roentgenologically, these lesions appear either as tracts of diffuse decalcification, with patches of condensed bone, or as excavations formed by the absorption of bone and containing connective or cartilaginous tissue with or without destruction of adjacent bone. Morphologic and serologic studies of the blood show no abnormality. Experience indicates that circulatory disturbances afford a basis for altered calcification and for necrosis of bone, and these are favored by changes in the somatic condition sufficient to affect calcemia, the condition of the blood vessels or the fibrinogenous function of the blood. Cure is spontaneous, but permanent deformities may result from compression.

VINTON, Brooklyn, N. Y.

BILATERAL SEROFIBRINOUS PLEURISY IN A TWO YEAR OLD CHILD. BERNARDO CARDELLE, Bol. Soc. cubana de pediat. **5**:119 (May) 1933.

The extensive bilateral pleural effusions in this case were treated by medical and hygienic measures. Considerable counterirritation was employed. This measure combined with rest in bed, fresh air and treatment with light effected a complete cure. Cardelle advises against thoracentesis except in those cases in which the fluid exudate causes great embarrassment of respiration or cardiac displacement.

SCHLUTZ, Chicago.

PULMONARY ABSCESS IN A CHILD OF FOUR YEARS. GABRIEL GOMEZ DEL RIO, Bol. Soc. cubana de pediat. **5**:127 (May) 1933.

The child presented the symptoms of pyemia with localization of one of the abscesses in the thoracic cavity. The abscess was demonstrated by injection of iodized poppy-seed oil 40 per cent. The abscess evacuated spontaneously through the bronchi. Surgical intervention is seldom necessary. The author recommends the intravenous use of a flavine dye or methenamine.

SCHLUTZ, Chicago.

GALLOP RHYTHM IN THE SEVERE ANEMIAS OF CHILDHOOD. LUIS MORQUIO, Bol. Soc. cubana de pediat. **5**:137 (May) 1933.

It is the opinion of Morquio that the gallop rhythm found in the essential anemias of childhood stands in direct relationship to the severity of the disease and follows the evolution of the condition of the blood. In the grave anemias it expresses a cardiac insufficiency. The cause of this phenomenon is to be looked for in fatty degeneration of the myocardium.

SCHLUTZ, Chicago.

PURE FORMS OF GRIP IN CHILDHOOD. P. NOBÉCOURT, Bol. Soc. cubana de pediat. **5**:153 (May) 1933.

Nobécourt prescribes comparatively simple measures for grip; warm baths or moist cold compresses to the chest, moderate doses of quinine or acetylsalicylic acid and ammonium acetate. For prostration he recommends the subcutaneous use of camphor. The accompanying rhinitis is treated with colloidal silver solutions and inhalations of medicated vapors. Bland diet and much fluid complete the treatment. He warns against brusque measures; they are contraindicated in the mild forms of grip and may do more harm than good.

SCHLUTZ, Chicago.

TWO CASES OF RETENTION OF URINE IN INFANTS. A. PUIQUERT GORRO, Paidoterapia **12**:31 (May) 1933.

Two cases of urinary retention in infants are reported. In one case the condition was due to congenital atresia of the urethra and to phimosis. Treatment

consisted in circumcision and meatotomy. In the second case the condition was due to hypospadias with a small external opening. This opening was dilated, and operative measures were carried out to cure the hypospadias. In both cases there was marked hypertrophy of the bladder. HERRON, Spokane, Wash.

FRAGILITAS OSSIUM. F. RODRIGO PALOMARES and JULIAN T. RUBIO, Pediatría españ. **22**:245 (April) 1933.

The authors believe that the terms "osteogenesis imperfecta" and "osteopsathyrosis" do not adequately describe the clinical picture and are too vague. They suggest the terms "periosteal aplasia" and "periosteal dysplasia," depending on complete absence of and pathologic change of periosteal ossification. They regard the syndrome of Kleinschmidt as periosteal aplasia and dysplasia combined with rickets. The anatomic substrate of periosteal aplasia is, in their opinion, a fundamental defect of primary formation.

The endocrine alterations sometimes observed in these cases are not a primary cause but a contemporaneous expression of mesoblastic alteration. The hereditary factor resembles that observed in other congenital malformations.

SCHLUTZ, Chicago.

AGRANULOCYTOSIS. F. POZZO and F. GAMES, Prensa méd. argent. **20**:1383 (June 21) 1933.

There are three types of agranulocytosis. The first is the pure form and appears in the course of certain pathologic conditions, such as arsenic poisoning, septicemia and endocarditis. The second form accompanies anemias, purpuras and hemorrhagic states, and the third may be caused by pathogenic organisms. In illustration of the latter type, a case is reported in a man, aged 26, who, following a severe attack of angina, had a white blood cell count of only 800. At autopsy Streptococcus perfringens and anaerobes were found. As an example of the first group, the author gives the history of a child, aged 12 years, who had a septicemia of twelve days' duration. The number of white cells fell to 2,500, of which only 22 per cent were polymorphonuclears. SANFORD, Chicago.

LOCALIZED OSTEITIS FIBROSA OF THE SUPERIOR MAXILLA. G. KRIEGSMANN, Arch. f. Ohren-, Nasen- u. Kehlkopfh. **137**:31 (Nov. 14) 1933.

Kriegsmann calls attention to the fact that osteitis fibrosa, which usually assumes a generalized form, may rarely be localized in the skull, especially in the superior maxilla. He reports a case of osteitis fibrosa of the superior maxilla in a girl, aged 15, in whom no osseous changes appeared in the rest of the skeleton. The patient exhibited swelling of the right cheek, which had developed gradually during the six months preceding the examination. The swelling was most severe 2 fingerbreadths from the right nostril. The soft parts were not edematous, red or sensitive to pressure and were mobile. The corpus of the maxillary bone protruded toward the front. In the canine fossa there was a smooth protuberance extending from the first premolar to the second molar. A roentgenogram of the nasal sinuses showed a strong, even clouding in the region of the right maxillary sinus. Introduction of fluid into the sinus could not be accomplished because of strong resistance. In a typical operation on the maxillary sinus performed because of a tentative diagnosis of osteosarcoma, it was found that the space usually occupied by the maxillary sinus was filled with spongy bone which was continuous with the walls of the sinus. The soft spongy bone was removed to form an opening the size of a normal maxillary sinus. Microscopically, the excised bone showed nothing suggestive of sarcoma, but presented a regular proliferation of osteoid tissue and active transformation characteristic of osteitis fibrosa. No exacerbation of the patient's condition has occurred in the four years since operation. Differentiation between osteitis fibrosa and osteosarcoma is possible only by microscopic examination. EDITOR'S ABSTRACT. [ARCH. OTOLARYNG.]

SOME CONSIDERATIONS ON THE PATHOGENESIS OF DIABETES INSIPIDUS. ALBERT SALMON, Schweiz. Arch. f. Neurol. u. Psychiat. **33**:95, 1933.

Diabetes insipidus is generally transitory following experimental injury of the tuber cinereum and may be lacking altogether when the entire floor of the third ventricle has been destroyed by disease. There are no constant relations, furthermore, between polyuria and either hypofunction or hyperfunction of the anterior lobe of the hypophysis. With the aid of numerous citations from the literature, Salmon seeks to account for these discrepancies. Normal urinary secretion, he assumes, is dependent on the existence of a proper balance between the respective functional states of the sympathetic and parasympathetic systems. In the presence of a lesion sufficiently extensive to destroy the hypothalamic centers of both systems, diabetes insipidus would, according to this hypothesis, be lacking. The vegetative equilibrium is further assumed to be related to a "hormonal equilibrium." After citing instances of an antagonism between the respective actions of solutions of pituitary and epinephrine, the author points out that the latter, when given in small doses, may act as a vasodilator and diuretic, particularly in vagotonic states or states of depressed sympathetic activity. Injections of epinephrine often aggravated a preexisting polyuria, and in cases in which the polyuria ceased in the terminal stages autopsy revealed changes in the suprarenal glands as well as in the hypophysis.

DANIELS, Denver. [ARCH. NEUROL. & PSYCHIAT.]

STENOSIS OF THE SPLENIC VEIN IN AN ELEVEN YEAR OLD GIRL. WILHELM ORN, Hygiea **95**:457 (June) 1933.

Orn presents in detail a case of obstruction of the splenic vein. Following a serious relapse splenectomy was performed with good results. Microscopic sections of the spleen and its vessels did not disclose the cause of the stenosis.

ELGHAMMER, Chicago.

PERITONITIS OR OSTEOMYELITIS? M. DE BRUIN, Maandschr. v. kindergeneesk. **2**:389 (May) 1933.

De Bruin reports two cases in which a very probable diagnosis of acute peritonitis was made in the beginning of the disease. The further course showed that the symptoms were caused by the presence of an osteomyelitic process near the pelvic cavity.

VAN CREVELD, Amsterdam, the Netherlands.

OXALURIA AND OXALATURIA. B. P. B. PLANTENGA, Maandschr. v. kindergeneesk. **2**:411 (June) 1933.

It is an old opinion that oxalaturia in which many crystals of calcium oxalate are present in the sediment of the urine is a symptom of a definite morbid picture called oxaluria of the oxalaturic diathesis. The excretion of large amounts of crystals of calcium oxalate may be combined with other abnormalities, especially functional disturbances of the nervous system. The conception of a special diathesis has been rejected. However, the author gives the history of a boy who, even on a diet poor in oxalic acid, excreted large amounts of this acid. Emotion and even slight infections caused an important rise in the amount of oxalic acid excreted so that there was an endogenous excretion of oxalic acid. However, reduction of carbohydrates in the diet, especially of sugar, caused an important decrease in the amount of oxalic acid excreted. Within ten years the author observed fourteen analogous cases in which carbohydrates had the same influence. He regards them as cases of constitutional oxaluria.

VAN CREVELD, Amsterdam, the Netherlands.

SERUM TREATMENT IN PNEUMONIA. A. B. F. A. PONDMAN, Maandschr. v. kindergeneesk. **2**:427 (June) 1933.

This article consists in a survey of the literature and a critical discussion. There is a decided difference of opinion in regard to serum treatment in pneumonia.

It is the author's opinion that treatment which is started in time and in which the serum is given in sufficient quantity is of some value in pneumonia of type I. In accordance with Wadsworth the author believes that it is not yet necessary to make use of purified serum. Intramuscular injections are preferred to intravenous ones. It is necessary to begin with from 40 to 80 cc. of serum. This amount should be given once more after twelve hours, and this treatment should be continued for from two to three days.

VAN CREVELD, Amsterdam, the Netherlands.

THREE CASES OF SPONTANEOUS PNEUMOTHORAX IN CHILDREN BELOW THE AGE OF ONE YEAR. S. M. C. VAN VEEN, Maandschr. v. kindergeneesk. **2**:461 (July) 1933.

Three cases of different types of pneumothorax are reported, in which the symptoms were also different. Case 1 was pneumothorax caused by shock in an infant with recurrent pneumonia; case 2, masked pneumothorax in a girl with bronchopneumonia and empyema. Case 3 occurred in a very young infant and arose from atelectasis. The difficulties of the diagnosis are discussed.

VAN CREVELD, Amsterdam, the Netherlands.

CHRONIC MYELOGENOUS LEUKEMIA IN A VERY YOUNG CHILD. J. C. SCHIPPERS, Maandschr. v. kindergeneesk. **2**:490 (July) 1933.

Schippers reports a case of chronic myelogenous leukemia in a boy, who was 15 months old when the blood was examined for the first time. The differential diagnosis is discussed.

VAN CREVELD, Amsterdam, the Netherlands.

DIFFICULTIES IN COUNTING THE RED CORPUSCLES IN A CASE OF MULTIPLE MYELOMA. F. L. J. JORDAN, Nederl. tijdschr. v. geneesk. **77**:1889 (April 29) 1933.

Jordan describes a case of multiple myeloma in which the process of counting the red corpuscles was difficult owing to the increased amount of blood protein which came into contact with the corrosive mercuric chloride contained in Hayem's solution (corrosive mercuric chloride, 0.5; sodium sulphate, 5; sodium chloride, 1; distilled water, 200).

VAN CREVELD, Amsterdam, the Netherlands.

RENAL DWARFISM. P. A. HEERES and L. KOSTER, Nederl. tijdschr. v. geneesk. **77**:3016 (July 1) 1933.

Heeres and Koster describe a typical case of renal dwarfism in a boy, aged 9 years. The only complaints were that the child had always been incontinent and had not grown during the last few years. In the hospital the renal function was found to be markedly disturbed; the urine was of low specific gravity and only now and then contained a small amount of albumin. The patient was very pale and was too small for his age. He showed deviations of the epiphyseal lines and abnormal values for blood calcium and blood phosphorus. There was no increase in the blood pressure. The picture was that of renal dwarfism. The syndrome of this disease is discussed at length.

VAN CREVELD, Amsterdam, the Netherlands.

Nervous Diseases

STUDIES IN ENDOCRINE THERAPY IN EPILEPSY. CALVERT STEIN, Am. J. Psychiat. **13**:739 (Jan.) 1934.

Cannon and Cushing have shown that the emotional element is frequently the precipitant of an epileptic seizure, also that one of the most frequent aura is of a visceral nature: a peculiar sensation in the epigastrium accompanied by a rapid

heart beat—a picture that is strongly suggestive of the early stages of traumatic shock. Thus, there is an unquestioned relationship between metabolism, the ductless glands, the autonomic nervous system and the emotions commonly affected in epileptic persons, and one might expect that the hormones of the ductless gland would have beneficial effects in the treatment of epilepsy. The endocrine products on the market today are inefficacious, because standardization is based on laboratory units and not on clinical findings.

The purpose of this study was to determine: (1) whether there was any specific endocrine disorder that appeared to be responsible for the production of epileptic seizures; (2) whether epileptic patients with accompanying clinical features of an endocrine disorder could be helped by treatment with any of the available endocrine preparations; (3) whether such patients, if clinically helped from an endocrinologic point of view, would also show a reduction in the frequency or intensity of their seizures, and (4) whether any of the available endocrine preparations had a specific effect empirically on seizures per se, regardless of the presence or absence of accompanying disorders in the endocrine system of the patients tested.

Sixty-eight epileptic patients in the Monson State Hospital for Epileptics (eight males) were studied for from six to eighty weeks. Seventy-five non-epileptic persons (including nurses and attendants—thirty-five males and forty females) served as controls. None of the endocrine preparations used proved specific, either in causing convulsions in the controls or curing the convulsions in the epileptic patients, although there was some evidence that in a few cases overstimulation of the ovaries (by extract of the whole ovary, or a combination) may be provocative of convulsions. The majority of the patients who received thyroid substance either alone or in combination with other gland extract showed clinical improvement in metabolism and general well-being. Pituitary, thyroid and suprarenal extract proved beneficial, though the results were not conclusive. Research along this line is being continued.

JAHR, Omaha.

THE CEREBROSPINAL FLUID AND THE CERVICAL LYMPH NODES. O. A. MORTENSEN and W. E. SULLIVAN, Anat. Rec. **56**:359, 1933.

The cerebrospinal fluid passes not only to venous sinuses, but also to the cervical lymph nodes. This has been demonstrated before by the use of brominized oil injected into the subarachnoid space of a dog after the removal of spinal fluid. Later, thorium dioxide was used. The authors repeated the work, using both these agents injected into the cisterna of an etherized dog; this was followed by roentgen examination. Brominized oil tends to stay at the base of the brain and cervical cord and five hours later appears in deep cervical lymph nodes. Thorium dioxide spreads rapidly over the whole surface of the brain, and within ninety minutes the cervical nodes are visualized. The material passes along the olfactory nerves to the nasal mucosa, and from here it probably runs in the subcutaneous lymph and posterior pharyngeal lymphatics to the submaxillary and deep cervical lymph nodes.

SNELLING, Toronto, Canada.

EVIDENCE FOR A CEREBRAL VASCULAR MECHANISM IN EPILEPSY. WILDER PENFIELD, Ann. Int. Med. **7**:303 (Sept.) 1933.

Penfield reports thirty cases of epileptic seizures in conscious patients who lay with one cerebral hemisphere exposed to view on the operating table. These patients were first studied to discover whether the attacks had a focal pattern; if so an osteoplastic bone flap was raised, and the brain was exposed. Following this, a convulsion was induced by stimulation. In forty-three operations in which electrical stimulation of the brain was carried out seizures were produced in all but thirteen cases. In thirty cases stimulation was followed by an aura and a local or general attack. During the seizure a common phenomenon was the arrest of visable pulsation in the cerebral arteries. The vessels were observed through magnifying lenses. Following the seizure the cerebral vessels pulsated violently and more rapidly than before the operation. More usually focal areas of cortical

anemia occurred. Six cases showed closure of one or more pial vessels, a constriction which shut off the vessel completely. Such constrictions remained for from fifteen to thirty minutes. The author concluded that the one constant visible phenomenon in the brain during an epileptic seizure is cessation of arterial pulsation and that in epilepsy the brain is subject to local vasomotor reflexes such as have never been described in the normal brain. Furthermore, these changes cannot be produced in experimental animals.

READING, Galveston, Texas.

HYPOTHALAMUS AND TEMPERATURE CONTROL. H. C. BAZETT, B. J. ALPERS and W. H. ERB, Arch. Neurol. & Psychiat. **30**:728 (Oct.) 1933.

Experiments were made with cats to check the modern conception that heat control is largely in the hypothalamus. It was found that the presence or absence of temperature control appeared to be associated with the preservation of the hypothalamus just cephalic to the corpora mamillaria; the area included the nuclei surrounding the walls of the third ventricle and the infundibular nuclei. Such animals did not, however, show a normal hyperpnea when exposed to excessive heat.

BEVERLY, Chicago.

CEREBRAL BLOOD FLOW PRECEDING AND ACCOMPANYING EXPERIMENTAL CONVULSIONS. F. A. GIBBS, Arch. Neurol. & Psychiat. **30**:1003 (Nov.) 1933.

The author investigated the influence of diminished cerebral blood flow on convulsions. The cerebral blood flow of cats before and after receiving convulsive agents was measured. The results were entirely negative.

BEVERLY, Chicago.

VENTRICULOGRAPHIC INTERPRETATION. ARNE TORKILDSEN and WILDER PENFIELD, Arch. Neurol. & Psychiat. **30**:1011 (Nov.) 1933.

The authors studied models of the human cerebral ventricles; they describe variations in normal encephalograms, which they found to be dependent on the portion of the ventricles filled with air and the angle from which the pictures were taken. Marked variation from the normal and errors in interpretation occur most frequently in anteroposterior views. The use of oxygen instead of air in taking encephalograms is recommended, because the severity of the reaction is less.

BEVERLY, Chicago.

PERICAPILLARY ENCEPHALORRHAGIA DUE TO ARSPHENAMINE: SO-CALLED ARSPHENAMINE ENCEPHALITIS. JOSEPH H. GLOBUS and SOLOMON W. GINSBURG, Arch. Neurol. & Psychiat. **30**:1226 (Dec.) 1933.

The authors report the results of detailed pathologic examination of two patients who died after a dose of arsphenamine. The outstanding pathologic picture was pericapillary hemorrhages. In view of these changes, it is suggested that there is no justification for the term "arsphenamine encephalitis" or "hemorrhagic encephalitis" but that the term "pericapillary encephalorrhagia due to arsphenamine" is more proper.

In the discussion of the article, Dr. Strauss of New York quoted Stokes as definitely stating that sulpharsphenamine is dangerous and he no longer uses it in the treatment of syphilis.

BEVERLY, Chicago.

PUNCTURE OF THE CISTERNA MAGNA; A MODIFICATION OF AYER'S METHOD, USED MORE THAN FIVE THOUSAND TIMES. L. H. GILMAN and G. F. KEMPF, Arch. Neurol. & Psychiat. **30**:1282 (Dec.) 1933.

The authors describe a modification of Ayer's method of cisternal puncture. They used this method in more than five thousand punctures and more than forty times on some patients. In this series one patient was seen at autopsy on whom

hemorrhage of the dura at the base of the brain may have been the result of puncture. The following points in the procedure are emphasized: (1) locating the depression below the occiput, the mastoid process and the normal hair line; (2) starting and keeping the needle in the exact midline directed at the hair line; (3) keeping the bevel directed caudally and removing the stylet as soon as the needle has passed through the outer tissues; (4) holding the needle with both hands and steadying the hands against the neck and head of the patient, and (5) starting the needle low (just above the epistropheus).

BEVERLY, Chicago.

CONDITIONED RESPONSES IN CHILDREN: A BEHAVIORAL AND QUANTITATIVE CRITICAL REVIEW OF EXPERIMENTAL STUDIES. GREGORY H. S. RAZRAN, Arch. Psychol., no. 148, April 1933, p. 1.

This monograph is the first of a series of comprehensive and critical reviews of experiments on human and animal conditioning and consists of an account of all the experimental work on conditioning of children. Emphasis is placed on behavior values, the facts of conditioning being treated as sets of variables of overt S-O-R (stimulus-organism-response) modifications, with no concern for cerebral theories involved. All data are subject to careful quantitative analysis, and attention is called to factors which were not controlled by the various experiments.

The experiments considered are those from both Russian and non-Russian sources and include investigations which were done in the laboratories of Krasnogorski, Chuchmarev, Lenz, Ivanov-Smolensky, and Bekhterev, as well as numerous individual studies. The material is carefully summarized, and conclusions and generalizations are drawn. A bibliography and diagrams of laboratories and apparatus are appended.

HAROLD ABRAMSON, New York.

THE INFLUENCE OF THE DIENCEPHALON AND HYPOPHYSIS UPON GENERAL AUTONOMIC FUNCTION. WILDER PENFIELD, Bull. New York Acad. Med. **9**:613 (Nov.) 1933.

This article is a scholarly discussion of the manifestations of dyspituitarism from the clinical angle, including a dissertation on the functions of the diencephalon (interbrain) and its significance in the metabolic disorders of man.

JAHR, Omaha.

THE TREATMENT OF POLIOMYELITIS. J. RUHRÄH, J. A. M. A. **100**:1587 (May 20) 1933.

Deformity is preventable in the management of the paralyses of poliomyelitis. The part should be kept at rest so long as there is hope of improvement in muscle power. The muscles that are protected from damage by stretching and fatigue by being placed in a position of relaxation, with the attachments brought as close together as possible, recover sooner and more completely. The patient should be kept recumbent, but in the same alinement as though be were standing erect. The bearing of weight should not be permitted during recovery, if crippling is to be minimized.

BONAR, Salt Lake City.

THE "GESTALT" OF THE DELINQUENT CHILD. CLAIRETTE P. ARMSTRONG, J. Abnorm. Psychol. **28**:87 (April-June) 1933.

The author is of the opinion that "delinquency does not spring upon society a finished product steeped in inherent criminal tendencies." The delinquent child is a product of his total environment, and he cannot be separated from his total configuration. Considered broadly, environment comprises not only the physical surroundings, but also the attitudes, implicit and explicit, of each member of the family to all other members. Environment may enhance or diminish personality traits, often modifying original traits beyond recognition. In the total situation (Gestalt) of the delinquent child many factors are involved, such as race and

nationality, whether the family is English-speaking, the economic level and mental status of the parents; the incidence of step-parents and of brothers and sisters; the rank of the delinquent among his siblings, and family pathology generally. Also of importance are the age of the delinquent child, the sex, the intelligence and the grading in school, the latter of which is nearly always misgrading, from the point of view of chronological or mental age or both. In addition, much is revealed concerning the total situation of the child by his type of delinquency.

The author remarks that investigation often reveals that the institutions on which society is built are functioning defectively. "Instead of an ounce of prevention we are meting out pounds of cure of uncertain adequacy and remedial measures which are but momentary palliatives." Attention is directed toward the urgent necessity of determining the etiologic factors underlying delinquent behavior.

ABRAMSON, New York.

STUDIES ON THE ETIOLOGY OF POLIOMYELITIS: ISOLATION AND CULTIVATION OF AN ORGANISM AND TRANSMISSION OF THE DISEASE IN MONKEYS. F. EBERSON, J. Lab. & Clin. Med. **18**:565 (March) 1933.

Berkefeld filtrates obtained from the nerve tissues of monkeys which had been inoculated with the virus of poliomyelitis and in which typical experimental poliomyelitis had developed were grown on special culture mediums under anaerobic conditions. Such cultures have been through the twentieth subplant. Inoculation of the organism from these cultures has produced typical poliomyelitis in monkeys, and recultivation of material from these infected monkeys has again yielded positive cultures. During certain stages of growth on the culture medium the organism developed into one which can be seen under high magnification. If this organism is injected into monkeys, typical poliomyelitis develops. Organisms recovered from the nerve tissue of such animals are invisible, but retain their power of infecting other animals by inoculation and of changing into a visible form on culture mediums.

MCMURRAY, Galveston, Texas.

CHANGES IN DISTRIBUTION RATIO OF CONSTITUENTS OF BLOOD AND SPINAL FLUID IN MENINGITIS. S. KOPETZKY and E. H. FISHBERG, J. Lab. & Clin. Med. **18**:796 (May) 1933.

In meningitis there is increased lactic acid, the cause of which is not definitely known. Also, the ratio of spinal fluid lactic acid to blood lactic acid increases, the normal never exceeding 1, while in meningitis this ratio is usually from 1.5 to 3.5. Along with this there is a decrease in the spinal fluid chloride content and a decrease in the spinal fluid chloride-blood plasma chloride quotient and lowering of the spinal fluid carbonate-blood plasma carbonate quotient. These changes lead to an increase in the buffer power of the spinal fluid carbonates, which helps to maintain an approximately normal p_H of the spinal fluid.

MCMURRAY, Galveston, Texas.

THE RELATION BETWEEN CEREBRAL DIPLEGIA AND BIRTH INJURY. T. D. GORDON, J. Michign M. Soc. **32**:165 (March) 1933.

Gordon stresses the probability of pressure exerted during parturition as the main etiologic factor in cerebral diplegia. He quotes Little as calling attention to this influence and stating that 75 per cent of his cases were due to difficult processes of labor. From Phillip Schwartz he quotes: "The brains of certain children dying soon after birth showed certain typically distributed hemorrhages, both sub dural and intra cerebral. . . . In cases of spastic diplegia lesions were found in exactly the same locations and distributions as the hemorrhages in early fatal cases."

The writer believes that hydrostatic pressure tends to force all the body fluids into the region of the presenting part during the uterine contractions and is an important factor in the rupture of small vessels within the brain. The area supplied

by the vein of Galen and its branches furnished most of the lesions found in spastic diplegia. Gordon hopes for a clarification of this subject through a more careful study of previous labors, more accurate observation of children during the newborn period, more skilful and complete autopsies on new-born infants and a "continuous strenuous program of education for the general practitioner, with closer cooperation between obstetricians, neurologist, the orthopedist and the pediatrician."

CAREY, Detroit.

NEUROCUTANEOUS SYNDROMES IN CHILDHOOD. HERMAN SCHWARZ and HAROLD ABRAMSON, J. Pediat. **3**:586 (Oct.) 1933.

Attention is called to three neurocutaneous syndromes: Recklinghausen's neurofibromatosis, Bourneville's tuberous sclerosis and angiomatosis of the brain associated with vascular nevi in the region of the distribution of the trigeminal nerve. The clinical manifestations of these three congenital disorders exhibit unusual similarity. The pathologic changes involve the ectodermal tissues such as the nervous system, the skin and the eyes. The cutaneous anomalies indicate associated maldevelopment in the central nervous system, as evidenced by convulsions and mental deficiency. Familial or hereditary tendencies occur in these three syndromes. Two cases of Recklinghausen's neurofibromatosis and one case of cerebral angiomatosis with nevi in the trigeminal region are reported.

LEMASTER, Evanston, Ill.

CEREBRAL ANGIOGRAPHY. EGAS MONIZ, Lancet **2**:1144 (Nov. 18) 1933.

Cerebral angiograms are obtained by means of an injection of from 10 to 16 cc. of thorium dioxide into the inferior part of the common carotid artery, between the two parts of the sternocleidomastoid muscle. The arteriogram is an important aid in the diagnosis of cerebral tumors. Aneurysms are easily diagnosed by angiograms. In order to obtain an arteriogram it is necessary to produce a flash of the roentgen tube a moment after the injection of the thorium dioxide.

This report is based on the study of three hundred patients who appeared to experience no untoward effects from the injections. Some excellent reproductions of roentgenograms of the skull outlining the blood vessels accompany the article.

LANGMANN, New York.

PATHOGENESIS OF MENINGOCOCCIC MENINGITIS. P. ZDRODOWSKI, Ann. Inst. Pasteur **50**:651, 1933.

Fatal meningitis was produced in rabbits by a subarachnoid injection of two billion freshly isolated meningococci. The virulence was quickly lost on serum medium, but was retained for several months when the organisms were transferred every two weeks on Dorset's medium. Very satisfactory viability (from two to three months) and virulence (from one to one and a half months) were maintained when a liquid egg medium under paraffin oil was used. Partially attenuated strains were reactivated by passage through animals, using either augmented doses or homologous endotoxin prepared by heating an emulsion at 100 C. The minimum lethal dose for a rabbit weighing 1.5 Kg. appeared to be between one and two billion organisms. The apparent virulence was dependent on the combined infectiousness of living organisms and the pathogenicity of toxic substance, which accounted for the relatively large dose needed.

FROM THE AUTHOR'S CONCLUSIONS.

APPLICATION OF THE OBSERVATION OF WEED IN THE TREATMENT OF BLOCKAGE OF THE CEPHALOSPINAL CANAL IN CEREBROSPINAL MENINGITIS. WLADIMIR MIKULOWSKI, Bull. Soc. de pédiat. de Paris **30**:705 (Dec. 20) 1932.

A boy, aged 11 years, had had repeated attacks of severe headache and vomiting since he was 1 year old. He was admitted to the hospital with the sixth attack, presenting a typical picture of meningitis. The first cerebrospinal fluid

obtained was clear and revealed nothing abnormal. Subsequently, meningococci were cultured from the cerebrospinal fluid. Only a few drops of fluid could be obtained by spinal puncture, and the injection of 10 cc. of air intrathecally did not break up the adhesions sufficiently to allow a freer flow of fluid. He was given 300 cc. of distilled water intramuscularly, and after an hour 30 cc. of clear fluid under increased pressure was removed by lumbar puncture. Antimeningococcic serum was administered intraspinally and intramuscularly. Fuchsin injected intramuscularly was not recovered in the spinal fluid one and a half hours later. The work of Weed and Kibben, who obtained a rise in the intracranial pressure after the intravenous injection of hypotonic solutions in animals and a fall in the pressure after the injection of hypertonic solutions, is reviewed. The boy was discharged from the hospital cured a little less than two months after admission. When he was seen two months later he was well and had had no further recurrence of meningeal symptoms. BENJAMIN, Montreal, Canada.

AVELLIS' SYNDROME. L. BABONNEIX, HALPHEN and WILM, Bull. Soc. de pédiat. de Paris **31**:82 (Feb. 21) 1933.

A girl, 15 years old, had a persistent cold and some difficulty in swallowing. The onset of the disorder dated back about seven months, when she had experienced tingling sensations about the head and the right arm and difficulty in talking. She was hoarse and had a nasal twang to her speech. There was some difficulty in swallowing, liquids being regurgitated through the nose. She had paralysis of the right half of the soft palate, slight weakness of the posterior pharyngeal wall and slight facial weakness on the right side. She was below normal physically and mentally. The Wassermann reaction of the spinal fluid was negative. The only explanation offered for the presence of the paralysis is that it might be due to hereditary syphilis.

BENJAMIN, Montreal, Canada.

VENTRICULAR INFECTION WITH THE BACILLUS OF FRIEDLAENDER. L. BABONNEIX and C. RIOM, Bull. Soc. de pédiat. de Paris **31**:84 (Feb. 21) 1933.

A boy, 21 days old, was taken ill with convulsions when 5 days old. He became gradually but progressively worse. There was little vomiting, and fever did not develop until some weeks after the onset of the illness. Lumbar puncture yielded a clear fluid, but ventricular puncture produced a purulent fluid which contained Friedländer's bacilli. There were hydrocephalus and marked dilatation of both ventricles, with some compression and destruction of the brain. The infant died about six weeks after admission to the hospital.

BENJAMIN, Montreal, Canada.

SPASMOPHILIA IN A BREAST FED INFANT, WITH CHARACTERISTIC SIGNS OF SPASMOPHILIA IN THE MOTHER. P. ARMAND-DELILLE, C. LESTOCQUOY, H. GAVOIS and O. MARCUS, Bull. Soc. de pédiat. de Paris **31**:86 (Feb. 21) 1933.

A girl, 19 months old, presented typical tetany. She was still breast fed and received little other food. The anterior fontanel was open, but there were no other signs of rickets. The mother, an Armenian, had tetany and had been subject to seizures which were apparently tetanic for the past five years. The baby's blood calcium was slightly low, but the mother's was a great deal lower. Both showed no abnormal response to electrical stimulation.

BENJAMIN, Montreal, Canada.

NASAL SUPPURATION AND LYMPHOCYTIC MENINGITIS. M. BALDENWECK, ROUÈCHE and LEVY-DEKER, Bull. Soc. de pédiat. de Paris **31**:122 (Feb. 21) 1933.

A girl, 3 years old, was admitted to the hospital because of swelling of the left ala nasi. There was a history of a fall a few days previously. The swelling

increased, involving the cheek and the lower eyelid on the left side, and there was marked swelling of the interior of the nose on the left. Fluctuation developed, and incision and drainage through the nose were performed. Roentgen examination at this time revealed cloudiness of the ethmoid and frontal sinuses on the left side. The child began to show signs of meningitis. Lumbar puncture yielded a clear fluid, which was under increased pressure and which contained a slightly increased number of cells, practically all of which were lymphocytes. No bacteria were found. The Wassermann reaction of the spinal fluid was negative. The swelling of the left side of the face subsided but the temperature remained elevated. A fixation abscess was produced; this was incised and drained. No pathogenic organisms were recovered from the pus. The temperature became normal within a few days. The child recovered and showed no signs or symptoms referable to the nervous system when observed a month afterward.

BENJAMIN, Montreal, Canada.

HERPETIC MENINGITIS IN CHILDREN. JOSÉ BONABA and SARAH RAYOLA, Arch. urug. de med., cir. y especialid. **1**:356 (Dec.) 1932.

Corneal herpetic vesicles can be transferred to the cornea of the rabbit and produce new herpetic vesicles. Some cases of herpetic meningitis present symptoms and lesions resembling those of encephalitis. A specific filtrable virus is the cause. The disease seems to be epidemic.

Herpes is a disease the virus of which has an affinity for the skin, the cornea and various parts of the nervous system. The authors report ten cases of herpetic meningitis in adults. The usual symptoms were severe headache, vomiting, fever, rigidity of the neck and positive Kernig and Brudzinski signs; the spinal fluid was at times clear and again turbid and contained from 50 to 500 pus cells, at times predominately lymphocytes and at other times polymorphonuclears. There were usually associated herpetic cutaneous lesions in various locations.

In four cases reported in children the symptoms were: an acute onset, with vomiting; headache; rigidity of the neck; usually a positive Kernig sign, and fever, as in acute meningitis. Herpes appears, usually on the lips, at, or a few days after, the onset. The mind remains clear, and there is rarely a positive Babinski sign, convulsions or stupor.

The spinal fluid is clear and is usually normal in all respects. The results of bacteriologic examination are negative. The prognosis is cure in every case, with no sequela. There is an absence of other etiologic factors. The diagnosis might be difficult if pneumonia were present in addition to the herpes, but with the clinical picture just described the diagnosis is not usually difficult to make, even though the disease is rare.

HERRON, Spokane, Wash.

ENCEPHALOGRAPHIC AND HEREDITARY INVESTIGATIONS IN IDIOPATHIC EPILEPSY. H. BOENING and T. KONSTANTINU, Arch. f. Psychiat. **100**:171 (July) 1933.

Boening and Konstantinu review the literature on idiopathic epilepsy with special reference to investigations concerning the etiology and pathology of the disease. They undertook an investigation of two aspects of the problem, namely, the search for signs of organic brain disease as demonstrated by pathologic encephalographic findings and the search for indications of hereditary factors. They selected from a group of 295 persons with epilepsy 97 who undoubtedly had so-called idiopathic epilepsy. Their observations were as follows: Half of the patients showed normal encephalographic pictures of the ventricular system. About the same proportion showed a normal encephalographic picture of the superior surface of the brain. Some with pathologic changes, however, overlapped a certain proportion of the group in which the ventricular system was normal, and vice versa. It was found that persons who have suffered with the disease for a long time tend to show more encephalographic defects than those in whom the disease has been of short duration. This tends to indicate that the defects that are demonstrated by encephalography may be results rather than conditions associated with the cause of the disease. No

relationship was found to exist between pathologic encephalographic findings and such clinical features as original feeblemindedness, epileptic deterioration or organic neurologic signs. In four cases convulsions were elicited by encephalography; no definite improvement was noticed in any case following the procedure.

The investigations into heredity showed the following results: Of the 420 siblings of the patients investigated, only 4.3 per cent suffered from epilepsy; 2 per cent were feebleminded, and 6.4 per cent were left-handed. No cases of typical migraine were found in any of the siblings. Thirty-two of the patients had children (94); of these, none showed definite epilepsy, but 15 were feebleminded. Study of the parents of the patients showed true epilepsy in only one father (0.52 per cent of all the parents). Of 793 collaterals studied, only 9 showed definite epilepsy, while 6 were suspected, and 1.06 per cent showed feebleminded-ness. Of the 388 grandparents, only 2 showed definite epilepsy, and 2 were suspected. The percentage of alcoholic addicts in all relatives was not appreciably different from that in the normal population.

MALAMUD, Iowa City. [ARCH. NEUROL. & PSYCHIAT.]

HYPERGLYCEMIA AFTER LUMBAR PUNCTURE. HERBERT SCHÖNFELD, Jahrb. f. Kinderh. **138**:174 (Feb.) 1933.

A moderate increase of blood sugar of brief duration was frequently observed by the author after lumbar puncture.

CLAUSEN, Rochester, N. Y.

THERAPEUTIC APPLICATION OF WEED'S EXPERIMENT IN SPINAL BLOCKADE CONSEQUENT TO MENINGITIS. WLADIMIR MIKULOWSKI, Jahrb. f. Kinderh. **138**:347 (March) 1933.

In a boy, aged 11 years, who had chronic meningococcic meningitis for a year, obstruction in the canal developed during the sixth exacerbation. The intramuscular injection of 300 cc. of distilled water so increased the intracranial pressure that the blockade was broken down, and serum could be used successfully. The patient was apparently well three years later.

CLAUSEN, Rochester. N. Y.

EXPERIMENTS ON SOCIAL CONDUCT IN THE FIRST YEAR OF LIFE. CHARLOTTE BÜHLER, Kinderärztl. Praxis **4**:8 (Jan.) 1933.

Bühler recounts some interesting social experiments on infants aged from 4 to 15 months. All infants in the first half year in their relations to other people are either passive or reactive to a definite external stimulus. In the second half year they become spontaneously active in their social relations. About the seventh month, rivalry toward another child definitely begins to make its appearance. The author found definite social types in infants under 1 year of age—types which are frequently encountered in older persons, but which had not been previously recognized at this tender age.

An infant of the socially blind type is so absorbed in the attainment of his immediate goal that he is scarcely conscious of the presence of the small partner who has been placed near him and completely ignores the partner. An infant of the despot type, on the contrary, is not socially blind, but is constantly aware of the presence of the partner. He grabs a toy from his companion, not because he wants it himself, but merely to show that he has the power to deprive the other of his possessions. The despot is preeminently a socially dependent type, since all his actions are undertaken for their effect on his companion. Another specially dependent type is the inhibited child who has no initiative and merely responds to the actions of his partner by hesitating imitation. He is constantly prepared to fit his mood to that of his companion. Another type is the socially independent infant who is willing to play with another child, but who is prepared to go his own way if the other is unreasonable or selfish. He maintains the freedom of initiative. That these definite types develop at so tender an age can only mean that there is an inborn, perhaps inherited, tendency in these children, but it does not

mean that such tendencies cannot be favorably altered by suitable environment and proper training. How to accomplish such alteration is the practical aspect of the problem.

HUENEKENS, Minneapolis.

THE TREATMENT OF PROGRESSIVE MUSCULAR ATROPHY AND MYATONIA CONGENITA. ERICH NASSAU, Kinderärztl. Praxis **4**:124 (March) 1933.

Nassau reports one case of progressive muscular atrophy and one case of myatonia congenita in which injections of epinephrine and pilocarpine hydrochloride were given alternately. Each patient was given ninety-three injections of these drugs, each drug being administered on alternate days. The dose of epinephrine was from 0.2 to 0.3 cc. of a 1:1,000 solution, and the dose of pilocarpine was from 0.1 to 0.3 cc. of a solution (0.025 Gm. diluted to 5 cc.), which equaled from 0.0005 to 0.0015 Gm. of this drug. In both cases favorable results followed quickly after the first few doses and were maintained three months after the cessation of treatment.

HUENEKENS, Minneapolis.

CLINICAL AND ANATOMIC EXAMINATION OF THE EAR IN A CASE OF INTERNAL HYDROCEPHALUS. H. BRUNNER, Monatschr. f. Ohrenh. **67**:1309 (Nov.) 1933.

Brunner reports the case of a girl, aged 10 years, who died of acute exacerbation of chronic internal hydrocephalus, which was not diagnosed until necropsy because the symptoms in most respects resembled those of lethargic encephalitis. The latter diagnosis was, however, contradicted by disturbances of the ocular muscles, the absence of rigidity, bilateral choked disks and the gradual loss of labyrinthine function. Microscopic examination disclosed that the cause of the focal symptoms was degenerative changes of the motor nuclei of the brain stem. Fresh otitis media existed in both ears. The labyrinths exhibited no changes attributable to hydrocephalus, such as stasis in the blood vessels, extravasations into the perilymphatic or endolymphatic spaces, degeneration of the sensory cells or dislocation of Reissner's membrane, despite pronounced cerebral edema. The cochlear function appeared to remain normal till death; at least the rapidly progressive increase of intracranial pressure produced no noticeable defect of hearing. This pressure resulted at first in vestibular hyperexcitability, but this changed later to hypoexcitability (absence of the rapid component of nystagmus). This case shows that the effect of increased intracranial pressure on the optic nerve is opposite to the effect on the acoustic nerve. The most severe changes in the optic nerve were found in the peripheral portion, while the central paths were spared. The acoustic nerve exhibited no peripheral changes, but the central paths of the vestibular nerve were diseased, resulting at first in hyperexcitability, then in hypo-excitability, of the labyrinth.

EDITOR'S ABSTRACT. [ARCH. OTOLARYNG.]

PARALYSIS OF THE UPPER PLEXUSES AFTER PROPHYLACTIC INJECTION OF SERUM. H. DEMME, München. med. Wchnschr. **80**:1502 (Sept. 29) 1933.

Demme reports a case of paralysis of the upper extremities following an injection of tetanus antitoxin for a lacerated wound of the thumb. Six days after the injection of the serum into the buttocks a serum rash appeared. Three days later, hypesthesia of both arms was followed by paralysis of both brachial plexuses. There was severe pain in the upper extremities for several days. There were no signs of meningeal irritation. Nine months later there were no sensory disturbances, but there were weakness of the muscles of the shoulders and arms and atrophy of most of the involved muscles.

BRAHDY, Mount Vernon, N. Y.

TRANSMISSION OF POLIOMYELITIS BY A BACILLUS CARRIER. K. KISSKALT, München. med. Wchnschr. **80**:1676 (Oct. 13) 1933.

The author reports a case of poliomyelitis in the family of a professor. The professor was called from the University of Tübingen to the University of Bonn at Easter 1922. His oldest daughter accompanied him. During the summer there

were cases of poliomyelitis in Tübingen. The professor's family frequently came in contact with one of the doctors at the hospital. None of the family became ill at the time. On August 3 the mother, three children and a maid joined the father and daughter. The eldest daughter became ill on August 21 with fever, drowsiness and diarrhea, and several days later extensive paralysis typical of poliomyelitis developed. No further cases occurred in the family or elsewhere in Bonn. No conclusion can be drawn from this case regarding the incubation period of the disease, because it is not known when the carrier infected the patient.

BRAHDY, Mount Vernon, N. Y.

CLINICAL IMPORTANCE AND DIFFERENTIAL DIAGNOSIS OF INFANTILE DEMENTIA (HELLER). WILLIAM LANGE, Ztschr. f. Kinderforsch. **41**:455 (July) 1933.

The article describes three cases of Heller's infantile dementia which were observed by the author. Since this disease is rather rare, he believes that a longer discussion is indicated. Characteristics of this disease, according to Zappert, are: (1) onset in the third or fourth year of life; (2) a striking disturbance of speech, which finally leads to total loss of function; (3) restlessness, excitability and conditions of fear; (4) increasing dementia, which leads to complete idiocy within a few months; (5) normal facies, despite the mental condition, and (6) absence of any other symptoms.

Corveri considers this form of dementia and amaurotic family idiocy as clinical expressions of the same process, which he regards as diffuse lipoid neurolysis. One of Lange's cases was in a uni-ovular twin. The other twin remained well, so that it is probable that Heller's dementia is not a congenital disturbance.

Only about twenty-four cases are described in the literature. This rarity is probably accidental, since the disease, when fully developed, may appear to be due to congenital idiocy or to the dementia of schizophrenia.

REICHLE, Cleveland.

ENCEPHALOGRAPHY; ITS DIAGNOSTIC SIGNIFICANCE IN THE TREATMENT OF CHILDREN. R. STANKIEWICZ and K. VINCENZ, Pedjatria polska **13**:1, 1933.

The credit for original work in encephalography goes to the American, Dandy, who first employed the procedure in 1919. Since that time the method is becoming more and more popular in diagnosis of abnormalities of the brain. The authors have devoted much time to this work; their experiments are described in an extensive article, in which they thoroughly explain the technic and give illustrations of several cases.

They dwell on the complications and sequelae of encephalography. The diagnostic procedure, according to them, is misleading; its technic therefore requires experience.

KRUPINSKI, Chicago.

ELECTRIC EXCITABILITY OF PERIPHERAL NERVES IN ARTIFICIALLY FED INFANTS. Y. KAWAKAMI, J. Pediat. (Tokyo), Nov. 20, 1933, no. 402, p. 1916.

The author found the electric excitability of forty artificially fed babies and divided them into five groups as follows:

	CC	AC	AO	CO	Comment
I.....	3.5	>5.0	>5.0	>5.0	Normal one month after birth
II.....	1.8	3.0	>5.0	>5.0	Normal
III.....	1.0	2.0	3.5	>5.0	Slightly abnormal
IV.....	0.7	1.5	1.2	>5.0	Moderately abnormal
V.....	9.7	1.5	1.2	<5.0	Markedly abnormal

The author also found increased excitability in rachitic babies, and this increase in excitability may be regarded as a sign of the disease. This phenomenon is present early in the course of rickets and hence may be used for diagnostic purposes.

KATO, Chicago.

EXPERIENCES WITH ENCEPHALOGRAPHY WITH SPECIAL REGARD TO THE INSUFFLATION OF AIR BY CISTERNAL (SUBOCCIPITAL) PUNCTURE. ERIK ASK-UPMARK, Acta psychiat. et neurol. **7**:22, 1932.

Encephalography and ventriculography were carried out on eighty-five occasions on seventy-six patients. The method employed in fifty cases was cisternal (suboccipital) puncture; in eighteen, lumbar puncture, and in fifteen, ventricular puncture. In twenty-seven cases epilepsy was diagnosed; in twenty-eight, tumor cerebri, and in twenty-one, other conditions, such as vascular lesions and pseudotumor cerebri. Pathologic conditions detectable by encephalography were present in forty-one cases, encephalographically normal conditions in twenty-seven and questionable conditions in seventeen.

Ask-Upmark concludes that the insufflation of air by cisternal puncture should be used as the normal method. It is less dangerous than ventriculography and lumbar encephalography; it is technically more simple than ventriculography and hardly more difficult than lumbar puncture; it is subjectively less disturbing than lumbar encephalography, and the roentgenograms obtained are at least as clear as those obtained by the injection of air into the spinal sac and essentially as satisfactory as those obtained by ventriculography.

Ventriculography should be used only if sufficient information cannot be obtained by suboccipital encephalography. However, the latter procedure has certain complications and dangers and for this reason should be used only if the usual neurologic and roentgen examinations do not establish a conclusive diagnosis. The complications are headache, vomiting and other phenomena, such as slowing and weakening of the pulse rate, changes in the color of the face and sweating. These seem to be due to meningeal irritation by the air and to increase in intracranial pressure. The intensity and duration of these complicating symptoms depend on three factors: (1) the method used (signs of meningeal irritation occur earlier and perhaps are more intense with the cisternal method, but occur, although they appear later, with the intraventricular); (2) the amount of air injected (this seems to produce a slighter reaction by the cisternal route than by the other two routes); (3) individual differences in susceptibility to reactions. The dangers may be due to: (1) trauma by the needle (e. g., puncture of large vessels), but this is none the less possible by the intraventricular route than by the cisternal, particularly if in the latter the needles are kept in the midline; (2) infection; (3) sudden changes in pressure (depending somewhat on the character of the case, cerebral tumor offering the greatest danger from this cause). Of fifteen patients in whom the intraventricular route was used, two died; of eighteen in whom the lumbar route was used, none died; and of fifty in whom the cisternal route was used, none died.

Encephalography gives valuable information in establishing the absence of pathologic processes in cases in which they are suspected and in revealing the presence of certain abnormalities, particularly distention of the ventricular system, displacement of the ventricular system or of the great fissures of the brain, defective filling of the ventricular system with air and cyst, which is demonstrated if filled with air.

PEARSON, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

Diseases of the Eye

THE ORTHOPTIC TREATMENT OF SQUINT. MONTAGUE L. HINE, Brit. M. J. **1**: 329 (Feb. 24) 1934.

Hine uses orthoptic treatment for children between the ages of 3 and 7 who have good fixation and a corrected vision of 6/18 or better in the squinting eye. As many squinters seem to obtain simultaneous vision or even fusion while the squinting eye still deviates as much as 10 degrees, Hine prefers a synoptophore for orthoptic training, because with this instrument the trainer can obtain an unimpeded view of the patient's eyes during the training. Convergent squints give the best results. Divergent squints not due to refractive errors are seldom helped. If after good binocular vision is obtained the squint persists, an operation should be

performed to approximate the visual axes. Hine thinks that operation under general anesthesia is contraindicated, except to prevent development of an inferiority complex in the child or the mother. A statistical analysis of the results of orthoptic treatment is not included in the article.

DUGGAN. [ARCH. OPHTH.]

ANGIOMATOSIS OF THE RETINA; RESULTS AND CONCLUSIONS. P. JUNIUS, Klin. Monatsbl. f. Augenh. **91**:747 (Dec.) 1933.

Junius gives a synopsis of the literature on angiomatosis of the retina, discusses each case briefly and attempts to compose some contradictory views. This study proves the existence of two types of retinal changes in this disease: there is either a predominance of newly formed vessels or a proliferation of cells resembling a tumor. Angiomatosis of the retina may remain benign up to an advanced age. In many of the patients the blood supply of the retina is disturbed as the result of a subnormal development or lack of the capillary net of at least a portion of the retina. Owing to malformations of the vascular system, vascular convolutions analogous to those in the retina occur in the cerebellum and cerebrum: A normal capillary net was absent in Dandy's patient, and a persistent vena capitis lateralis was present in a patient of Yates-Paine, both conditions apparently representing embryonal malformation. The fundamental condition for the development of angiomatosis of the retina, in some cases at least, seems to be congenital absence of blood vessels in one or several areas of the retina. The compensatory impulse of the organism results in the preservation of embryonal blood vessels which normally disappear and the formation of neoplasms.

Histologic examination reveals the occurrence of numerous capillaries, with the lumen filled with endothelial cells. In the retina the fundamental factor is the angiomatosis, no matter what secondary development may result.

Junius accepts Roussy's and Oberling's division of the angiomatous tumors into three types: (1) cavernous tumors (the hemangiomas of Cushing and Bailey), which occur in all parts of the brain, (2) angiomas of the reticulo-endothelial type (the hemangioblastomas of Cushing and Bailey) and (3) angiogliomas (the intercolumnar hemangioblastomas of Cushing and Bailey). Tumors of the second type, of interest in this connection, have been found in the central nervous system and in the retina. They are formed not by simple vascular epithelium, as are the ordinary angiomas, but by reticulo-endothelial tissues. Secondary changes may entirely transform their structure. Stasis of the lymph may lead to lipolipoid transformation of the cells, and xanthomatous transformation of the reticulum may result. Berger and Vallée reported a case of angioreticuloxanthoma of the retina.

Several problems remained unsolved. Junius could not explain why Viets' patient experienced no discomfort from the changes in the cerebellum and from angiomatosis of the retina, which had existed for several decades, but suffered an exacerbation only in his eye when he was 44 years of age. Equally uncertain remained the etiology of the development of vascular convolutions in the retina and the brain.

STOLL. [ARCH. OPHTH.]

HEMORRHAGIC TUMORS OF THE ORBIT. M. I. AVERBACH, Russk. arch. oftal. **8**:808, 1932.

The conditions favoring orbital hemorrhages are discussed by Averbach at length and are grouped as follows: hemophilia, scurvy, general vasomotor disturbances, organic diseases of the walls of blood vessels, stasis with hypertension, and trauma. He adds to all the cases reported in the literature certain ones of his own in each group. He reports two cases of unilateral exophthalmos in which the condition was clinically diagnosed as orbital tumor but which at operation proved to be hematoma. He purposely, therefore, omits the usual term "cyst of the orbit" for such tumors. One of the patients gave the history of a gradual protruding of the right eyeball for seven years. Examination showed ptosis, exoph-

thalmos and limitation of movements of the eye upward. A soft, elastic tumor was palpated at the upper orbital wall. All tests and the roentgenogram failed to contribute any information of importance. A neoplasm was suspected. The patient was operated on, and his recovery was uneventful. The content of the tumor was a reddish-brown liquid. Under the microscope sections showed an abundance of round cells, infiltration and granulation tissue. There were numerous erythrocytes, hemosiderin, cholesterol and a dark pigment that gave a positive reaction for iron. The second case resembled the first in every respect. In both cases the wall of the cavity facing the orbit had its own fibrous membrane, while the wall facing the bone had no relation with the periosteum. The conclusion is drawn that in both cases a subperiosteal hemorrhage occurred in the upper orbital wall which after a long time underwent a series of complicated changes, partly inflammatory and partly degenerative or atrophic.

SITCHEVSKA. [ARCH. OPHTH.]

THE DIAGNOSIS OF NEVI OF THE CONJUNCTIVA. E. T. BIONTOWSKAYA, Sovet. vestnik oftal. **2**:88, 1933.

A man, aged 30, stated that he had had a brown spot on the left eye since childhood. The spot had increased in size considerably for the past two months. A pigmented nevus with an abundance of blood vessels encroaching on the cornea was present. A melanosarcoma was suspected, and the eye was enucleated. The pathologic examination showed a polymorphous character of growth. There were three definite groups of cells. One group resembled connective tissue cells; these were richly pigmented and accumulated near the blood vessels. The second group could be classified morphologically as endothelial cells. The third group, close to the cornea, resembled carcinomatous epithelial cells with little pigment and blood vessels. Biontowskaya analyzes the main theories as to the origin of nevi; he believes that his microscopic observations of this neoplasm combined the evidence advanced for these theories. It is important to excise as much tissue as possible in order to find all three groups of cells and to make a correct diagnosis of the histogenesis of nevi.

SITCHEVSKA. [ARCH. OPHTH.]

CYANOSIS OF THE RETINA IN CERULEAN DISEASE. N. A. PLETNEVA, Sovet. vestnik oftal. **3**:253, 1933.

Two young female patients suffered from congenital stenosis of the pulmonary artery. There was general cyanosis *(Blausucht)* of the skin and of all the visible mucous membranes. Polycythemia with a high hemoglobin index (158 per cent and 112 per cent) was recorded for the patients. The lids were cyanotic; the conjunctival vessels were distended and of violet hue. The vision and the pupils were within normal limits. The fundi presented characteristic changes. The retinal veins and arteries were greatly distended; all small vessels were visible; the disks were hyperemic, and the retinas were dark violet blue. The diagnosis was cyanosis retinae due to congenital defect of the right side of the heart.

SITCHEVSKA. [ARCH. OPHTH.]

AN ORBITAL HEMORRHAGE WITH VOMITING. Y. TUTUI, Acta soc. ophth. jap. **36**:115 (Sept.) 1932.

A boy, aged 15 years, received a blow on the eyebrow, which resulted in an orbital hemorrhage, followed by repeated vomiting for two days. Examination of the vegetative nervous system gave the following results: The reactions to epinephrine, pilocarpine and atropine and the Aschner phenomenon were positive. This showed sensitiveness of the entire vegetative nervous system and a mixed form of sympathicotonia and vagotonia. The vomiting is explained by the trigeminal vagus stimulation in the form of an oculogastric reflex in which vagotonia played a certain rôle.

In another case of prolonged vomiting after exenteration of the eyeball there was a large effusion of blood into the scleral cup. The vomiting was produced by pressure on the nerve stumps of the trigeminal nerve in the sclera and acted as an oculogastric reflex.

KNAPP. [ARCH. OPHTH.]

Diseases of the Skin

SILK SENSITIVITY. K. D. FIGLEY and H. J. PARKHURST, J. Allergy **5**:60 (Nov.) 1933.

The authors report five cases of atopic eczema due to sensitivity to silk, in which the silk exerted its effect as an inhalant rather than as a contactant. They believe that in the cases in which wearing silk may have caused contact dermatitis the irritant was some substance with which the silk was weighted or dyed rather than the silk itself. Reagins could be demonstrated in each of their cases, but contact patch tests performed with various preparations of silk gave negative results. All five patients had other manifestations of atopy, such as asthma or symptoms resembling hay fever.

CARO, Chicago.

THE CAUSE OF DEATH IN INFANTILE ECZEMA. A. B. SCHWARTZ, J. Pediat. **4**:172 (Feb.) 1934.

The causes of death in ten infants who died after admission to the hospital for treatment of eczema included septicemia (in four cases), fulminating bronchopneumonia (in two) and intestinal intoxication (in two). In none was there an enlarged thymus. The author warns against the hospitalization of infants with eczema, because of their susceptibility to severe infectious processes.

LEMASTER, Evanston, Ill.

CALCINOSIS UNIVERSALIS AND DERMATOMYOSITIS. COUNCILL C. RUDOLPH, J. Pediat. **4**:342 (March) 1934.

A case of calcinosis universalis in a 9 year old boy is reported. An illness, which was diagnosed as dermatomyositis, occurred previous to the deposition of calcium in the tissues. There are many references to the literature on this subject.

LEMASTER, Evanston, Ill.

ERYTHRODERMIA DESQUAMATIVA. LEWIS WEBB HILL, J. Pediat. **4**:436 (April) 1934.

Twenty-one cases of erythrodermia observed by the author are discussed. In this condition the entire surface of the skin is red and somewhat moist, and usually there is considerable scaling. Frequently, the hands and feet are cold, blue and clammy. Boric acid ointment was found to be the best remedy for local application. The best results in treatment were obtained by a diet high in protein and low in carbohydrate and fat, such as partially skimmed milk with added carbohydrate and casein. The author considers erythrodermia to be a symptom complex occurring in seborrheic and eczematous infants, but not a distinct disease.

LEMASTER, Evanston, Ill.

SIMPLIFYING THE PROBLEM OF INFANTILE ECZEMA; AN ANALYSIS OF 157 CASES. LEE BIVINGS, J. Pediat. **4**:494 (April) 1934.

One hundred and fifty-seven cases of eczema in infants, who were treated by the author, are reported. Skin tests by the scratch method are strongly advised in this condition and are considered to be reliable. Milk, eggs and cereal were the foods most commonly found to cause signs of sensitization. The author's chief principle in treatment was that of removing the offending food from the diet. Local treatment consisted of the application of white petrolatum only. Complete recovery occurred in 78.5 per cent of the infants.

LEMASTER, Evanston, Ill.

ARACHNOIDISM OF SPIDER BITES. N. O. EADDY, J. South Carolina M. A. **30**:9 (Jan.) 1934.

Three cases of arachnoidism caused by the bite of Latrodectus mactans, or the black spider, are reported. Medical textbooks are prone to omit sufficient data regarding this condition. There are twelve deaths on record from the bite of this insect. The symptoms are marked by restlessness and acute paint in the back and abdomen, with much rigidity in the abdomen.

WESTON JR., Columbia, S. C.

PERSONAL EXPERIENCES IN THE PROPHYLAXIS AND TREATMENT OF RINGWORM OF THE HANDS AND FEET. EARL D. OSBORNE, EDWIN D. PUTMAN and RAYMOND J. RICKLOFF, New York State J. Med. **33**:1270 (Nov. 1) 1933.

The pupils of the Buffalo High School were required to walk through rubber pans containing 1 per cent sodium hypochlorite. There has been a marked reduction in ringworm. The general treatment is discussed.

AIKMAN, Rochester, N. Y.

CHRONIC LYMPHATIC EDEMA. J. W. STRUTHERS, Edinburgh M. J. **41**:27 (Feb.) 1934.

A girl, aged 8 years, had suffered since the age of 2 years from edema of the entire left leg as far up as the inguinal ligament in front and the gluteal fold posteriorly. The cause was obscure. The condition had been associated for several years at least with imperfect calcification of the corresponding bones of the leg and those of the left half of the pelvis, as shown by roentgenograms. The author could find no report of a smilar case.

NEFF, Kansas City, Mo.

PELLAGRA IN GREAT BRITAIN. HUGH S. STANNUS and CHARLES R. GIBSON, Quart. J. Med. **3**:211 (April) 1934.

The case of a girl, aged 7 years, who suffered from pellagra, is described in detail. In addition, the authors present a summary of all the published reports of cases of pellagra which have appeared in Great Britain. A photograph illustrating the reported case is presented.

BRADFORD, Rochester, N. Y.

ABORTIVE ACRODYNIA. M. APERT and LICHTENBERG, Bull. Soc. de pédiat. de Paris **31**:71 (Feb. 21) 1933.

A boy, 5 years old, had repeated spells of terror, in which he became hysterical and cried out that he felt abnormal sensations, at times referred to his mouth and at other times to his extremities. These would cease within a short time, to recur after shorter or longer intervals. Between the intervals he was perfectly normal. It is considered that he had abortive and atypical acrodynia, although he showed few of the signs and symptoms characteristic of this disease.

BENJAMIN, Montreal, Canada.

TUBERCULOUS ETIOLOGY OF ERYTHEMA NODOSUM. RAUL CIBILS AGUIRRE, Arch. argent. de pediat. **4**:697 (Oct.) 1933.

The author is of the opinion that all forms of erythema nodosum are tuberculous in origin and are always the result of infection with the bacillus of Koch. The appearance of the disorder signifies an important stage in the infection. He believes that a critical study and painstaking investigation of doubtful cases will invariably demonstrate tuberculosis as the causative agent.

SCHLUTZ, Chicago.

CHRONIC TROPHEDEMA OF MEIGE. FLORENCIO BAZAN and HERTA OTTE, Arch. argent. de pediat. **4**:727 (Oct.) 1933.

The authors report a case of this rather rare condition, which is known in the English and American literature as Milroy's disease, in a child aged 13 years.

Chronic edema of the neurotrophic type involved both legs entirely, the left leg being affected more than the right. The edema had existed since birth. There was considerable mental defectiveness, and spastic hemiplegia and strabismus were present. The upper extremities showed considerable atrophy of disuse. No form of therapy used was effective in improving or relieving the disorder.

SCHLUTZ, Chicago.

SCLEREMA-LIKE CHANGES IN THE SKIN. KARL RUPILIUS, Arch. f. Kinderh. **101**:91 (Jan. 31) 1934.

The clinical picture and pathology of sclerema, scleroderma and scleredema are discussed. A case of scleredema in a 20 month old boy is reported. The fundamental pathologic picture consists in chemical and physical changes in the colloids of the subcutaneous connective tissue. The etiology has not been definitely established.

LEMASTER, Evanston, Ill.

CAPILLARY MICROSCOPY IN ERYTHEMA NODOSUM. DENES V. MORITZ and EMIL V. LEDERER, Arch. f. Kinderh. **101**:101 (Jan. 31) 1934.

The capillary changes in fifteen cases of erythema nodosum in children were studied throughout the course of the disease. All the children showed positive tuberculin reactions. The changes in the capillaries of the nodules of erythema nodosum were similar to the changes in the capillaries of the skin at the site of a positive tuberculin reaction. These observations support the assumption that the two reactions are of similar etiology.

LEMASTER, Evanston, Ill.

FAMILIAL JUVENILE ACANTHOSIS NIGRICANS. SWEN HELLERSTRÖM, Acta dermat.-venereol. **14**:88 (June) 1933.

Hellerström reports a case of familial juvenile acanthosis nigricans associated with severe diabetes mellitus. The endocrine character of the condition—the patient also had cutis verticis gyrata—is apparent, since the condition of the skin as well as the metabolic condition showed decided improvement following total castration.

SCHORR, Chicago. [ARCH. DERMAT. & SYPH.]

IMPETIGO BULLOSA NEONATORUM. H. J. T. HIEMCKE, Maandschr. v. kindergeneesk. **3**:223 (March) 1934.

This article is an extensive discussion of this acute, infectious disease of the new-born, with special stress on the bacteriologic side of the problem. Twenty cases were studied. Staphylococci were always found in these cases. A detailed description of some cases, with histologic reports, is given.

VAN CREVELD, Amsterdam, The Netherlands.

SCLEREDEMA, SCLEREMA ADIPOSUM AND DIFFUSE SCLERODERMA IN BABIES. T. J. HALBERTSMA, Maandschr. v. kindergeneesk. **3**:263 (April) 1934.

The author discusses the symptomatology and differential diagnosis of these diseases, based on the observation of fourteen cases, and reports a case of diffuse scleroderma in a child aged 10 months, in whom the deviations were already present at birth.

VAN CREVELD, Amsterdam, The Nertherlands.

SEBORRHEIC ECZEMA. T. M. VAN LEEUWEN, Nederl. tijdschr. v. geneesk. **77**: 3644 (Aug. 12) 1933.

The author reports a case of seborrheic eczema in a boy, aged 5 months, and discusses the symptoms, etiology and therapy, especially from a dermatologic point of view.

VAN CREVELD, Amsterdam, The Netherlands.

ERYTHEMA NODOSUM. G. J. VAN DEN BOVENKAMP, Nederl. tijdschr. v. geneesk. **78**:407 (Jan. 27) 1934 .

Eleven cases of erythema nodosum, eight of which were accompanied by tuberculous infection, are reported. The assumption of a causative interrelation presents itself, which need not be contradicted by the incidence of erythema nodosum in rheumatic fever. The erythema nodosum is believed to occur only if certain qualities of the infecting agent coincide with a certain disposition of the host.

VAN CREVELD, Amsterdam, The Netherlands.

Surgery and Orthopedics

A REVIEW OF MODERN TREATMENT OF BURNS. J. PEYTON BARNES, Arch. Surg. **27**:527 (Sept.) 1933.

The author discusses the treatment of burns based on a review of two hundred and five patients treated during the last thirteen years. The routine procedure in the initial treatment of burns as advocated by him is worthy of a detailed account. A 10 per cent solution of tannic acid is kept on hand at all times. Morphine is given to all patients with burns. The skin around the burned area is cleaned with ether, and if grease has been applied as first aid to the burn this is gently washed off with ether; the loose skin is trimmed off, and the area is covered with sterile sheets. The patient is placed in bed on sterile sheets; the cradle and lights are put in place, and spraying with tannic acid is begun. A hypodermoclysis of 1,000 cc. of saline solution is given promptly and is repeated every eight hours. The burned area is sprayed every fifteen minutes for the first twelve hours, then once an hour for twelve hours, after which no spraying is done. The temperature under the cradle is kept at from 98 to 100 F. Water is given freely by mouth. Daily estimations of the hemoglobin are made in every case. The rise of hemoglobin is the most accurate ready clinical method of estimating the concentration of the blood. Hemoglobin of 125 per cent indicates a precariously high concentration of blood, and hemoglobin of 140 per cent and over indicates a blood so concentrated that fatal collapse is imminent. In extensive burns there are two stages in which transfusion of blood is beneficial. In primary shock the transfusion is given usually within from ten to twenty hours after the burn. In secondary toxic shock transfusion should be given after the first two or three days, if the toxemia is increasing. In severe cases transfusion should be given at the first untoward sign; exsanguination-transfusion is probably the ideal procedure. KAISER, Rochester, N. Y.

EFFECT OF COMPLETE AND PARTIAL STARVATION ON THE RATE OF FIBROPLASIA IN THE HEALING WOUND. E. L. HOWES, HARRY BRIGGS, RICHARD SHEA and S. C. HARVEY, Arch. Surg. **27**:846 (Nov.) 1933.

In an attempt to determine whether the healing of wounds is affected by complete or partial starvation, the authors utilized young and old rats. The strength of the wounds of the stomach made in animals fed various diets was tested, and certain deductions were made. In adult rats the rate of return of healing strength in wounds of the stomach was not appreciably affected by complete starvation or by giving one half the required amount of an adequate diet. On the other hand, the healing of wounds in the stomach of young rats was decidedly retarded by giving only one half the required amount of an adequate diet.

KAISER, Rochester, N. Y.

DIAGNOSIS AND TREATMENT OF FRACTURED SKULLS. LOUIS T. WRIGHT, JESSE J. GREENE and DAVID H. SMITH, Arch. Surg. **27**:878 (Nov.) 1933.

Three hundred and forty-seven consecutive cases of cranial and intracranial injuries were studied. The symptoms were tabulated, and those of greatest diagnostic value are stressed. Various therapeutic procedures are discussed. Lumbar

drainage proved of little value and is not advocated. Lumbar drainage combined with limitation of the intake of fluid did not appear to help the patients. In only eighteen cases were operations performed; these were all cases of compound depressed fractures. The study confirms the work of other investigators showing that nonoperative treatment of fractured skulls is the best treatment known today.

KAISER, Rochester, N. Y.

THE AGE OF CHOICE FOR OPERATIONS OF CHOICE IN INFANCY AND CHILDHOOD. THOMAS H. LANMAN, J. Pediat. **4**:107 (Jan.) 1934.

It is advocated that no surgical measures be carried out on children under 2 years of age, unless there are definite reasons for not postponing the operation. However, if the condition requiring operation is not compatible with normal development of the child, earlier operation is needed. An indirect inguinal hernia can usually be treated conservatively with a woolen yarn truss until the child is about 2 years old, when operation is advisable. Even large umbilical hernias can be strapped with adhesive tape till the child is 1½ years old, before surgical intervention is needed. Small hydroceles of the tunica vaginalis are best left alone. If the hydrocele extends up the spermatic cord a hernia is usually associated, and operation is indicated after the age of 2 years. If the child's condition is good, operation for harelip is performed between the ages of 3 and 5 weeks. Repair of a cleft palate, whether or not this is associated with harelip, is best done between 18 months and 2 years of age. In spina bifida with little or no paralysis, operation may be performed at any time during the first few weeks of life. Undescended testes are operated on when the patient is from 8 to 10 years old. Hypospadias may be corrected between the ages of 5 and 10 years, depending on the pathologic condition. Exstrophy of the bladder is treated by transplantation of the ureters into the rectosigmoid when the patient is from 3 to 5 years of age. Necessary surgical procedure should not be postponed because of the early age of the child, but there should be a clear indication for any operation performed during the first two years of life.

LEMASTER, Evanston, Ill.

ORTHOPEDIC TREATMENT OF INFANTILE PARALYSIS. EZRA A. JONES, New England J. Med. **209**:831 (Oct. 26) 1933.

Treatment of infantile paralysis should begin immediately after the diagnosis is made. Even within the first few days the weight of the bedclothes will stretch the anterior tendons; placing pillows under the knees will start flexion deformities in the knees and hips; while slightly propping up the patient in bed has started deformity. Heat and perfect immobilization will usually relieve this.

The second stage in this treatment is carried out in the convalescent stage. This begins after a period of from six to eight weeks, when all the tenderness has disappeared and some power has returned to the muscles. This is the time when training of muscles and massage may be instituted.

The third stage comes after several months have elapsed and one is able to tell which muscles will probably not have return of power; steps should be taken to prevent the occurrence of deformity by weight-bearing or antagonizing muscular pull. In this class also fall the neglected cases in which deformity has developed and operative procedures are necessary.

GENGENBACH, Denver.

CHRONIC DUODENAL OBSTRUCTION. ROSS GOLDEN, New York State J. Med. **33**:819 (July 1) 1933.

The importance of roentgen examination in this condition is emphasized. An obstruction at the junction of the first and second portions of the duodenum due to a duodenal band is reported in a baby 7 days of age. An operation was successful, and the child made a good recovery.

AIKMAN, Rochester, N. Y.

PEDIATRIC DIAGNOSIS OF ORTHOPEDIC CONDITIONS. ARMITAGE WHITMAN, New York State J. Med. **33**:930 (Aug. 1) 1933.

The author gives a general review of orthopedic conditions in small children. Torticollis, if detected early, can be easily overcome by systematic daily manipulations. Bowlegs and knock knees have largely disappeared, owing to the preventive treatment of rickets. If children were taught to walk properly, much foot trouble would be avoided.

AIKMAN, Rochester, N. Y.

OBSERVATIONS ON ABDOMINAL CONDITIONS IN CHILDHOOD. SAMUEL AMBERG, Wisconsin M. J. **33**:31 (Jan.) 1934.

Increasing symptoms of partial intestinal obstruction appeared in two children. In the first case these symptoms were of six years' duration and followed an abdominal injury. In the second case they were of seven months' duration; there was no history of injury. From 4 to 5 feet (121.9 to 152.4 cm.) of dilated atonic bowel consisting of ileum and jejunum was found in each case at operation. There was no mechanical obstruction, but a paralytic ileus was found. Resection relieved both patients. Disturbances of the involuntary nervous mechanism is blamed.

Two other children, aged 7 and 6 years, respectively, had acute obstruction from intussusception. In the first case the condition followed a ruptured appendix, and there were repetitions of the obstruction, necessitating six operations, with final resection of the ileocecal coil. Ileocolostomy and enterostomy were valuable aids in recovery. The condition of the second child was unfavorable. Enterostomy was performed, and supportive treatment was instituted; the invaginated intestine eventually sloughed by rectum between the fifth and twelfth day following the operation.

Another child became purpuric during measles; she passed 15 cc. of bright blood rectally. Besides the hemorrhagic state, a Meckel's diverticulum with mucosal hemorrhage was observed post mortem.

JANNEY, Wauwatosa, Wis.

CONGENITAL DILATATION OF THE COLON TREATED BY DIVISION OF THE LUMBAR SYMPATHETIC CORD. HUGH T. ASHBY and D. M. SUTHERLAND, Brit. M. J. **2**:1069 (Dec. 9) 1933.

The authors report a case of congenital dilatation of the colon in a patient who was operated on at 2½ years of age. The operation consisted in lumbar sympathectomy during which the second, third and fourth left lumbar ganglions were excised. Constipation was relieved, but the colon has remained the same size.

ROYSTER, University, Va.

PRELIMINARY COMMUNICATION ON THE TREATMENT OF PNEUMOCOCCAL EMPYEMA BY ASPIRATION AND INJECTIONS OF TAUROCHOLATE OF SODA. A. P. THOMSON, Proc. Roy. Soc. Med. **26**:1538 (Oct.) 1933.

The author reports four cases of pneumococcic empyema which were treated successfully with injections of a 20 per cent solution of sodium taurocholate.

WILLIAMSON, New Orleans.

A CASE OF BURNING WITH ELECTRICITY IN A CHILD. CECIL P. G. WAKELEY, Proc. Roy. Soc. Med. **27**:27 (Nov.) 1933.

A boy, aged 6, ventured across an electric railway and came in contact with the live wire. The whole body was immediately doubled up in spasm, and the patient fell with his right arm on the wire. He was removed by a pole hook and taken to the hospital in extreme shock and suffering from severe burns of the right and left arm and the left leg. He made a good recovery. Skin grafts were used after healthy granulations formed over the burnt areas. The grafts took well.

WILLIAMSON, New Orleans.

MYCOTIC INFECTION OF VERTEBRAE. M. YVIN, Rev. d'orthop. **21**:42 (Jan.-Feb.) 1934.

The case is reported of a girl, 16 years of age, who was admitted to the sanatorium complaining of pain in the region of the left hip. No clinical evidence of disease could be found. Roentgenograms were normal. The temperature ranged between 37.3 and 38.3 C. (99.1 and 100.9 F.). The general condition was good. Eighteen months later, a small gibbosity appeared over the ninth dorsal vertebra. A roentgenogram showed destruction of the eighth, ninth and tenth dorsal vertebrae and partial destruction of the left femoral head. These lesions apparently cleared up, and the patient was not seen again until three years later, at which time no further evidence of disease was noted. Six years after the onset of her first illness, she was readmitted to the sanatorium. At this time the deformity over the ninth dorsal vertebra was still present, and a second swelling was seen over the fourth and fifth dorsal vertebrae. Roentgenograms showed destruction of these vertebrae; in addition, the left pulmonary area was obscured by a dense shadow which occupied almost the whole area, extending outward from the spine. A comparison with previous roentgenograms showed that this shadow had been present at an earlier date, but had been of less extent. Examination of the sputum gave negative results for Bacillus tuberculosis on several occasions. Numerous staphylococci were seen on the slides. Inoculation of guinea-pigs gave negative results. The patient died eight months after admission. Postmortem examination of pus from the abscess showed the presence of fungus growth (Monilia).

RYAN, Vancouver, Canada.

INDICATIONS OF SPLENECTOMY IN VARIOUS HEMATOSPLENIC SYNDROMES OF INFANCY. MAMERTO ACUÑA, Arch. argent. de pediat. **4**:309 (May) 1933.

Acuña reports a series of cases in which splenectomy was performed successfully. This procedure is indicated in cases of hemolytic icterus, Banti's disease and thrombopenic purpura haemorrhagica. It is not indicated in the pseudoleukemic types of anemia.

In hemolytic icterus it is the best treatment. It is successful in the early periods of Banti's disease, but not so reliable in the later periods. In thrombopenic purpura haemorrhagica the effect is uncertain, sometimes being good; again, there is no effect whatsoever. Splenectomy is practically ineffective in pseudoleukemic anemia, except in chronic cases.

The mortality from the operation varies between 4 and 8 per cent. It is higher the younger the infant.

SCHLUTZ, Chicago.

FRACTURE OF THE ELBOW WITH SEVERE MOTOR DISTURBANCES OF THE HAND FROM EXTERNAL CAUSES. EMILIO ROVIRALTA, But. Soc. catalana de pediat. **4**:49 (April-June) 1931.

The author reports a case of Volkmann's paralysis following fracture of the elbow and tight bandaging.

WATSON, Elmhurst, Ill.

URINARY STONES IN CHILDHOOD. ERNST ALBRECHT DIETRICH, Arch. f. Kinderh. **101**:26 (Dec. 19) 1933.

A 4½ year old girl had had urinary symptoms since 1 year of age, which consisted chiefly of polyuria, polydipsia, pain before urination and recurrent attacks of abdominal cramps. The urine contained some albumin, many leukocytes and an occasional red cell. The patient had been treated for pyelitis until admission to the hospital, where roentgenograms of the abdomen showed both kidneys to be studded throughout with many small stones. The author stresses the fact that urinary lithiasis in childhood may produce an atypical clinical picture and suggests that the condition may be more frequent than is commonly thought.

LEMASTER, Evanston, Ill.

VITAMINS AND HEALING OF WOUNDS. HANS-JOACHIM LAUBER, Beitr. z. klin. Chir. **158**:293, 1933.

The author tried to show experimentally that the addition of small doses of vitamin A to the diet causes acceleration of the healing of wounds. In larger doses, no definite change was noted, and in very large doses there was retardation of healing.

The addition of vitamins D, B or C has no effect on the healing of wounds.

RUBIN, Boston.

AMBULATORY TREATMENT OF CONTRACTED FLATFOOT. W. SCHINDLER, Med. Klin. **29**:1442 (Oct. 20) 1933.

By means of Böhler's unpadded plaster of paris cast which allows the patient to walk, Schindler successfully treated fourteen patients with flatfoot caused by muscular contraction. The cast should be light, should be inspected frequently within the first day or two in order to avoid circulatory disturbance or impairment of movements of the toes and should be worn about six weeks. Frequently the muscles are stronger after removal of the cast than on its application. The treatment does not always obviate the necessity of radical intervention. This procedure is described in L. Böhler's "Technik der Knochenbruchbehandlung," Wilhelm Maudrich, Vienna, 1933.

DOOLEY, Kent, Conn.

TREATMENT OF EMPYEMA IN CHILDREN. M. J. DEINUM, Maandschr. v. kindergeneesk. **3**:47 (Nov.) 1933.

A survey of different treatments of empyema in childhood is presented. Treatment by resection of the ribs in 154 cases gave a mortality of 10.4 per cent. The indications against resection of the ribs are mentioned.

VAN CREVELD, Amsterdam, The Netherlands.

ACUTE APPENDICITIS IN INFANTS. E. PETTERSEN, Norsk mag. f. lægevidensk. **95**:296 (March) 1934.

Two cases of acute appendicitis are reported in infants aged 18 and 23 months, respectively. In both cases purulent peritonitis was present, which cleared up after appendectomy.

TOVERUD, Oslo, Norway.

Miscellaneous

THE CHEMICAL COMPOSITION OF SALIVA AND BLOOD SERUM OF CHILDREN IN RELATION TO DENTAL CARIES. REBECCA B. HUBBELL, Am. J. Physiol. **105**:436 (Aug.) 1933.

Analyses were made of the saliva and blood serum of fifteen children who were free from caries and of seventeen who had active caries. These children were from 9 to 16 years of age. The carbon dioxide capacity of the saliva of the children free from caries was about 44 per cent higher than that of the saliva of children of the same age who had active caries. The titratable alkaline of the saliva of the children free from caries was about 24 per cent higher than that of the children of the same age who had active caries. In other respects, analyses of the saliva (determination of the total solids, ash, calcium, phosphorus, chloride, diastatic activity and p_H) showed no consistent differences between the two groups. The blood serum calcium, inorganic acid-soluble phosphorus, carbon dioxide capacity and p_H were the same for the children of both groups.

NOURSE, Cleveland.

"RED BACK" SPIDER BITE AND MAGNESIUM SULPHATE TREATMENT. CESAREO DE ASIS, Am. J. Trop. Med. **14**:33 (Jan.) 1934.

The author gives a brief description of the red back (Latrodectus aasseltii) spider and shows how it differs from the black widow spider. A brief review of the

experimental work on the potency of the venom of the Latrodectus aasseltii is also reported. The symptoms of the red back spider bite are enumerated by the author as follows: (a) elevated blood pressure, (b) slow and often weak pulse, (c) rapid and often labored respiration, (d) profuse perspiration, (e) general weakness and numbness, (f) pain in the muscles and (g) paralysis. The author states that the poison is potent and may prove fatal. It seems to have a special predilection for the peripheral nerves and nerve endings rather than for the central nervous system. Magnesium sulphate in a 25 per cent solution injected intravenously is efficacious and is recommended for trial in the bite of the black widow spider, as the symptoms are similar.

BURPEE, Augusta, Ga.

THE TREATMENT OF SEXUAL UNDERDEVELOPMENT IN THE HUMAN MALE WITH THE ANTERIOR PITUITARY-LIKE HORMONE OF URINE OF PREGNANCY. D. L. SAXTON, Endocrinology **18**:47 (Jan.-Feb.) 1934.

This report deals with thirteen boys, aged from 10 to 21 years, having genital underdevelopment as the chief disorder, who were treated with intramuscular injections of the anterior pituitary-like hormone of the urine of pregnant women.

Eleven were obese. All responded to the treatment by an increase in the size of the external genitalia and appearance of the secondary sexual characteristics, while in two, who were thin, the condition did not yield to treatment. In six of these boys cryptorchidism was present at the start, and in four of these six the testes became localized in the scrotum after treatment. Those treated intensively with 300 units given five days per week improved more strikingly than those in whom it was not feasible to give such frequent injections. Photographs of five of the boys illustrate the improvement which occurred.

JACOBSEN, Buffalo.

PEDIATRICS AT THE HARVARD MEDICAL SCHOOL. KENNETH D. BLACKFAN, J. Pediat. **4**:114 (Jan.) 1934.

Blackfan describes the facilities available for the pediatric department of Harvard Medical School, with reference to buildings and equipment, outpatient departments, cooperation with other departments of the school and with organizations dealing with children, the personnel of the departmental staff, opportunities for research, services for house officers, residents and graduate students and the curriculum offered to undergraduate students.

LEMASTER, Evanston, Ill.

DIURETICS AND THEIR USES. D. MURRAY LYON, Brit. M. J. **2**:853 (Nov. 11) 1933.

This article consists in an interesting discussion of water balance and imbalance, an outline of all the approved diuretics with their physiologic action and a discussion of the indications for the use of each. It does not lend itself to brief abstracting.

ROYSTER, University, Va.

ON THE NATURE OF HIGH ARCHED PALATE. O'C. O'SULLIVAN, Brit. M. J. **1**:800 (May 5) 1934.

The author discusses the frequency with which high-arched palate is found in the presence of evidences of vitamin D insufficiency. He then discusses briefly the mechanical forces which might cause arching of the palate or narrowing of the alveolar arches. He states that in these cases there is little or no encroachment on the antrums and further states that there is no elevation of the palate, the apparent height of the roof being due entirely to abnormal downward elongation of the alveolar process. Development of the roof of the mouth is discussed in order to explain this formation. There are, however, certain types of this condition which are apparently congenital. These, he thinks, are due to persistence of a state of fetal development.

ROYSTER, University, Va.

THE PRE-SCHOOL CHILD. EDITORIAL, M. J. Australia **2**:855 (Dec. 23) 1933.

Children need individual attention during the preschool period, and their welfare cannot be best promoted by group examinations in summer "round-up" or similar clinics. The problems of each child are complicated and are best handled by the general practitioner in the seclusion of his consulting room. As the public is not sufficiently aware of the dangers of this age period in regard to malnutrition, deficiency diseases, infectious diseases, diseased tonsils and adenoids, carious teeth, abnormalities of the eyes, defects of speech, emotional and behavior problems and other disorders, the medical profession should make an organized effort to teach parents the necessity of seeking advice for preschool children at regular intervals.

GONCE, Madison, Wis.

REGARDING THE WORK OF DR. BARTALINI ON THE DETERMINATIONS OF THE BODY SURFACE. C. CISI, Riv. di clin. pediat. **31**:965 (Aug.) 1933.

Observations made in the Pediatric Clinic at Genoa confirm the studies of Bartalini (*Riv. di clin. pediat.* **31**:591 [May] 1933; abstr., AM. J. DIS. CHILD. **48**:637 [Sept.] 1934), who selects the method of Du Bois as being the most satisfactory for determining the body surface.

HIGGINS, Boston.

THE FUNDAMENTALS IN THE REARING OF THE CHILD. FRANZ HAMBURGER, Arch. f. Kinderh. **101**:212 (March 31) 1934.

In this article Hamburger discusses the principles which he considers it important to observe in the proper education and management of children. The parent must, of course, set a good example for the child. Overindulgence and too strict discipline must be tempered by love for the child and an understanding of his faults and virtues alike. The importance of teaching good habits early in life is emphasized. Disobedience in a child is attributed to the faulty training imposed by the caretakers rather than to the child. The dangers inherent in the rearing of an only child are discussed. Disagreements between parents should never be aired before children. The author makes no claim to presenting any original or new advice. He has tried to collect and restate those policies which experience and knowledge of child psychology have shown to be of greatest value in teaching the child to become adjusted to his environment.

LEMASTER, Evanston, Ill.

LEAD POISONING IN A BABY. E. GORTER, Maandschr. v. kindergeneesk. **3**:135 (Jan.) 1934.

A case of lead poisoning in a baby, aged 4 months, is reported. It was caused by an ointment containing lead, which was applied to the mother's breast and not removed before the breast feedings. The methods of diagnosis are discussed in detail. In this case a roentgenogram of the bones showed the typical deviation. The lead could be demonstrated in the urine by studying the emission spectrum of the ashes of the urine.

VAN CREVELD, Amsterdam, The Netherlands.

Society Transactions

NEW YORK ACADEMY OF MEDICINE, SECTION OF PEDIATRICS

Nov. 8, 1934

HARRY BAKWIN, M.D., *Chairman*
ALEXANDER T. MARTIN, M.D., *Secretary*

PREVENTION OF COMMON CONTAGIOUS DISEASES WITHOUT QUARANTINE ON THE PEDIATRIC SERVICE OF FIFTH AVENUE HOSPITAL. DR. WILLIAM H. PARK, DR. CAMILLE KERESZTURI and DR. DAVID HAUPTMANN.

In the twentieth century, under the influence of Charles V. Chapin, belief in propagation of disease by the air was shattered. Terminal gaseous disinfection was abandoned in the case of all diseases except typhoid fever and smallpox.

There is still one practice in which physicians do more than is necessary; this is the observance of strict quarantine rules.

In order to test the value of hospital quarantine a study of three years' duration was undertaken in the children's service of Fifth Avenue Hospital. During this

Contagious Diseases in the Pediatric Service of Fifth Avenue Hospital From June 11 to July 1, 1931

Disease	Number of Outbreaks	Immunized Patients			Control Patients		
		Total Number	Cross-Infected		Total Number	Cross-Infected	
			Number	Per Cent		Number	Per Cent
Rubella	2	22	..	....	26	..	....
Scarlatina	5	38	..	....	37	..	....
Pertussis	10	96	..	....	90	..	....
Parotitis	4	65	..	....	93	1	1.07
Varicella	2	47	5	10.6	80	1	1.2
Morbilli	6	125	9	7	83	21	25
All diseases	29	393	14	3.5	409	23	5.6

period no quarantine was enforced, so that admissions and discharges were uninterrupted.

Instead of quarantine and strict aseptic technic, specific convalescent serum was used for prophylaxis against all common contagious diseases in half of the susceptible population of the ward. The usual precautions against the spread of infection were used.

The results of the study were as follows:

1. No secondary cases occurred in German measles, whooping cough or scarlet fever.

2. The chickenpox convalescent serum appeared to be of no value.

3. Serum from patients convalescing from mumps decreased the development of parotitis from 2.8 to 0, and serum from patients convalescing from measles decreased the incidence of cross-infection of measles from 25 to 7 per cent.

4. The order of frequency of cross-infections was: first, measles; second, chickenpox, and third, mumps.

5. Of 1,717 patients admitted to the hospital, 37, or 2.1 per cent, became infected while in the hospital.

6. Only 47 per cent of the population of the ward were susceptible to the contagious disease to which they were exposed.

7. The rate of cross-infection of the susceptible patients was 4.6 per cent.

8. The lack of quarantine and of aseptic technic apparently did not increase the rate of cross-infection of our pediatric service. In 1930, when strict quarantine was adhered to, the rate for all children of cross-infection was 2.2 per cent.

9. It was concluded that the disadvantages of quarantine for a general pediatric service are greater than the good achieved by its use.

PEDIATRICS AND PUBLIC HEALTH. DR. JOHN L. RICE, Commissioner of Health.

In New York City, because of the decline in the birth rate and the marked restriction of immigration, the child population is becoming smaller, not only in proportion to the entire population, but actually smaller in numbers. Thus, an increasing number of pediatricians will find a constantly decreasing clientele.

Of approximately 100,000 babies born in the city each year, slightly more than 5,000 die during the first year of life. But about half of these deaths occur during the first month and so are largely the responsibility of the obstetrician rather than of the pediatrician. During the ensuing years of childhood the death rate drops rapidly; nevertheless, from the end of the first month to the fifteenth year more than 6,000 deaths occur, with pneumonia as the leading cause of death and accidents second.

The Department of Health has a distinct responsibility in this field; thus, it must assure an adequate and safe supply of milk; it must control the spread of the communicable diseases of childhood; it must provide diagnostic laboratory facilities and specific biologic products for prevention and treatment; through its preschool and school medical services it must direct the attention of parents to physical defects in children, and in the case of the indigent it should see to it that facilities for the correction of such defects are provided. Finally, when the child leaves school to take up remunerative employment the department should safeguard his health by making sure that he has no physical defects which would make him unfit to compete with others.

It is not always possible to draw the line between the responsibility of the Department of Health, on the one hand, and the pediatrician and the general practitioner on the other. Thus, in the immunization against diphtheria the Department of Health must endeavor to have all children receive this protection. So far as possible, the Department of Health prefers to have the actual immunization done by private physicians, and the more that private physicians undertake this work the more can the services of the Department of Health be made available for other pressing activities. Similarly, in the physical examination of school children, we have tried to get private physicians to do a greater share of this work. Our regulations provide that each child entering school for the first time shall present a certificate showing the results of an examination by a licensed physician. There is reason to believe that private physicians do not keep track of the children among their clientele as much as they might, for it is our experience that parents are grateful if, from time to time, they receive a reminder of things which should have their attention, for example, when the child is 6 months of age a reminder regarding immunization against diphtheria, some time later a reminder regarding vaccination against smallpox and at 5 years a reminder of the required health examination and correction of physical defects. Such a procedure would help the Department of Health a great deal, for it would reduce the work which it is now compelled to do.

We now operate seventy-three Baby Health Stations at which mothers are instructed in the care of babies. Approximately 40 per cent of the babies born in New York City are under the supervision of these stations. It seems to me that this is too large a proportion and indicates, I believe, that private physicians have not sufficiently organized their work to render service to well babies. In its popular health education the Department of Health is constantly emphasizing

the importance of this health supervision, and private physicians might well make greater use of this education of the mothers. Perhaps we should help physicians become familiar with the service we give at our Baby Health Stations, a service which mothers evidently desire. Perhaps we should arrange to open up one or two year appointments at these stations to young physicians who have just finished an internship. In this way the stations would serve as training centers in pediatrics. I should like to have the views of the members on this suggestion.

At present the Department of Health is gradually pushing forward the idea of the health center. It is anticipated that within a year or so seven new buildings will be provided. The central idea is to bring the Department of Health and health activities closer to the persons it attempts to serve. These centers will be chiefly educational, localizing the clinics of the department. We wish them to be of help to the physicians in the districts. We desire the advice of the members in the planning of programs.

The 1,700,000 children in New York City are entitled to as good health service as we can give them. They need curative medicine and a much larger measure of preventive medicine; they need to have stronger environmental safeguards; they need more help in normal development, and they and their parents need more information regarding health. In this whole program the pediatrician and the Department of Health need to work close together.

CHICAGO PEDIATRIC SOCIETY

Regular Meeting, Nov. 20, 1934

STANLEY GIBSON, M.D., *President, in the Chair*

ESSENTIAL (THROMBOCYTOPENIC) PURPURA HAEMORRHAGICA. DR. BERNARD MYERS, London, England.

My first experience with this disease was about thirty years ago in London. A girl, aged 10 years, who suffered from purpura haemorrhagica had been treated in the hospital by rest in bed and good feeding for two months. She was then allowed to be up and was told that she could walk. After taking a few steps, she fell dead by the side of the bed. At autopsy an internal hemorrhage was found to be the cause of death.

A second patient with a somewhat similar condition was seen in the same hospital about a month later, and the outcome was equally unfortunate. These cases early impressed me with the gravity of this disease.

I had 5 patients with this disease, and after all ordinary methods of treatment, including blood transfusion, had failed, I arranged to have splenectomy performed. All the operations were done by my colleague, Dr. Maingot.

The first patient, Winnie B., aged 10 years, was admitted to the Royal Waterloo Hospital in July 1925, suffering from purpuric spots on the body and limbs, associated with numerous small bruises and continuous bleeding from the gums and nose.

All the ordinary methods of treatment were tried, including the injection of hemoplastic serum, but without avail.

The spleen was not palpable. The red blood cells numbered 3,900,000 per cubic centimeter; with 45 per cent hemoglobin; the white blood cells numbered 5,000. No platelets were seen.

The bleeding time was twenty minutes, and the results of the capillary resistance test were positive. Careful examination showed no primary cause. The case was evidently one of essential thrombocytopenic purpura haemorrhagica, and as all methods of treatment had failed I asked my surgical colleague to perform splenectomy.

The second patient, Mrs. E. D., was admitted to the hospital in 1909 as a girl of 13½ years, with a history of a black-red rash which had appeared all over

the body. There was a previous history of free bleeding from the mouth and nose, and she had an effusion of blood under the sclerotic of the right eye.

She continued to come to the hospital for many years because of purpuric symptoms, which caused her great inconvenience. I first saw her in September 1924. She was then married and had been lately confined; the uterus, however, continued to bleed for several weeks, in spite of the most careful treatment by the obstetricians. Finally she was referred to the medical department, and it was found that she had a typical case of purpura haemorrhagica, with markedly positive results of the capillary resistance test, a bleeding time of fifteen minutes and a thrombocyte count between 40,000 and zero. The blood coagulation time was two minutes and twenty seconds. She looked distinctly ill, and the number of red cells fell to nearly 2,000,000. Transfusion of 160 cc. of blood (0.25 per cent citrated) was given. The result was dramatic: The patient showed great general improvement, and all bleeding ceased within twenty-four hours. She left the hospital a fortnight later.

For some years she had suffered from menorrhagia, which frequently necessitated admission to the hospital. This condition persisted, and as her life was almost miserable I advised splenectomy.

The third patient, Albert E. W., aged 6 years, was admitted to the hospital in February 1926, with a history of purpura haemorrhagica for a month. He suffered from bleeding from the gums and bowel and from hematuria. Petechiae were present on the arms, legs and palate, and there were free hemorrhages in the mouth.

The bleeding time was fifteen minutes; the capillary resistance test gave positive results, and no platelets were seen. This case was obviously one of essential thrombocytopenic purpura haemorrhagica, and splenectomy was performed.

This case, like all my other cases, was the only one that had occurred in the family concerned.

The fourth patient, Joyce M., aged 6 years, was admitted to the hospital in July 1931, with purpuric spots on the limbs and continuous oozing of blood from the nose and gums, which did not yield to treatment.

The bleeding time was one and a half hours; the capillary resistance test gave positive results, and the platelets numbered 16,000 per cubic centimeter.

Because of my previous experience in case 1, I arranged to have splenectomy performed.

The fifth patient, Edith W., aged 10 years, was admitted to the hospital during November 1932, under the service of my colleague, Dr. Hugh Dunlop, who asked me to collaborate with him in dealing with the case.

The patient suffered from petechiae and ecchymoses on the trunk and limbs and also had continuous epistaxis and bleeding from the lower lip.

The bleeding time was at first eleven minutes, (afterward fifteen minutes); the blood platelets numbered 25,000, and the results of the capillary resistance test, though negative at first, became positive later.

After a few weeks paralysis of the left arm and leg and some weakness of both eyes developed. These disturbances completely cleared up within a few weeks, but bleeding from the gums and the lower lip continued, and I strongly advised splenectomy.

The following points may be noted:

Four of the 5 patients were females, and 1 was a male. The ages at which the first symptoms were noted were as follows: in case 1, 9 years; in case 2, 9 years; in case 3, 6 years; in case 4, 6 years, and in case 5, 9 years. The ages when splenectomy was performed were: in case 1, 10 years; in case 2, 28 years; in case 3, 6 years; in case 4, 6 years, and in case 5, 11 years. The duration of the symptoms at the time of operation were: in case 1, one year and four months; in case 2, over seventeen years; in case 3, one month; in case 4, four days, and in case 5, one year and seven months. Cases 3 and 4 were acute cases, and cases 1, 2 and 5 were chronic.

In case 1 nine years have elapsed since splenectomy; in case 2, eight years and ten months; in case 3, eight years and nine months; in case 4, three years and four months, and in case 5, one year and five months. There has been no return of purpuric symptoms in any of the 5 cases since splenectomy. Ordinary knocks have caused no bruising since splenectomy, in contrast with the severe and easy bruising previously. At present the health of all the 5 patients is perfect. Patient 2, who suffered from severe menorrhagia previous to splenectomy, has had normal menstruation since; in patient 1 menstruation has begun since splenectomy; it is always normal and never excessive.

It will be interesting to recall here a case of Henoch's purpura which I saw about six years ago. A girl, aged 6 years, had been sent to us from Trinidad, with the history that since the attack severe hematuria had remained. Briefly, all treatment to cure the bleeding from the kidneys was unavailing, and finally I advised splenectomy. This was done, and the bleeding ceased. Was this a case of Henoch's purpura which went on to purpura haemorrhagica of the kidneys?

I shall cite only a few statistics. The librarian of the Royal College of Surgeons of England informed me that the total number of cases of essential thrombocytopenic purpura haemorrhagica for which splenectomy had been performed that he was able to trace was 233. In these 173 patients had been cured; 30 had died; 1 had been incompletely cured; 17 had improved; 6 were unimproved, and in 6 the results were unknown.

With regard to the pathogenesis, I cannot accept the view that this is essentially a disease of the capillaries, as the capillaries cease to bleed after splenectomy. Further, the platelet count, which may have been exceedingly low, quickly rises to a figure between 100,000 and 300,000 and finally seems to settle down at about from 120,000 to 150,000. In short, I would suggest that this is a disease caused by a toxic substance of some kind present in the spleen, and that the good results obtained by splenectomy are due to the removal of the toxic substance.

A number of cases of recurrence of purpura after splenectomy have been reported, but these were probably due to the presence of accessory spleens which had not been removed. We made a point of looking for and removing accessory spleens; they were present in 53 per cent of the cases. In one case a splenulus was carefully examined and showed pathologic changes similar to those of the parent spleen.

At the Royal Society of Medicine in London a surgeon stated that he operated on a patient with acholuric jaundice, with good results for six months, after which the symptoms recurred. He then reopened the abdomen and found that an accessory spleen had grown to nearly full size. This was removed, and since then the symptoms have completely disappeared and have not recurred after several years.

In 2 cases we had the number of thrombocytes in the splenic artery and vein estimated; in 1 case the number in the latter was one fifth and in the other case one third of those present in the artery.

In a patient with secondary purpura in whom merely passing the hand across the chest produced marked bruising the thrombocytes were estimated at my suggestion before bruising and fifteen minutes afterward. The number of thrombocytes was 300,000 in each instance; therefore the bruising did not reduce the number of thrombocytes present in the blood in this particular case.

I think that splenectomy is better treatment than tying the splenic vessels.

Concerning the diagnosis, one has to differentiate the condition from hemophilia, aplastic anemia, lymphatic leukemia, scurvy, hereditary and hemorrhagic telangiectasis and also from symptomatic purpura and hereditary thrombasthenic purpura.

Finally, one has to remember the possibility that bleeding from the gums, epistaxis, hematuria, menorrhagia, melena and other conditions may be due to essential purpura haemorrhagica, and, in my opinion, if the diagnosis is definitely established and the condition is proved to be primary, the appropriate treatment is splenectomy.

All will agree that the spleen should by no means be looked on as a useless organ, but rather as a most valuable one, which at certain times of life is appar-

ently essential to the body; but, like the tonsils or appendix, it should be removed if there is definite proof that it is the source of a serious disorder gravely interfering with the health.

I should like to see the following experiments carried out: (1) A study might be made of the effect of an extract made from an excised spleen of a patient with essential thrombocytopenic purpura haemorrhagica on a guinea-pig or rabbit to see if purpura results. Again, (2) the serum from a patient with an active case of essential thrombocytopenic purpura haemorrhagica might be injected into an animal and the effect watched. Should purpura result, some serum from the same patient might be injected into the same animal or a similar animal when the patient has no symptoms indicative of purpura and the results compared. (3) Would the preserved serum from a patient with an active case cause purpura if injected into the patient himself during a quiescent period? (4) Similar experiments with preserved serums taken during active and nonactive periods might be performed on the splenectomized patient himself a few weeks after operation.

DISCUSSION

DR. ISAAC A. ABT: The president, Dr. Gibson, has already said that this has been an interesting, inspiring and inclusive address. It has been the custom in learned and medical societies in America, as it probably is in those abroad, that the address of a distinguished invited guest remain undiscussed. I have been requested, however, to comment on Dr. Myers' paper. He had a great deal of material on the history of this disease, but for want of time he omitted that part of the address. If the members will allow me a few moments I shall supplement his address with reference to some of the persons who first observed and described the various phases of purpura.

Of course the ancients had a knowledge of purpura, but they were confused as to its nature and origin. In medieval times physicians confused purpura with scurvy. The first person to write a clinical description of purpura was Paul G. Werlhof, in the early eighteenth century. He was a great personality and was born in Helmstädt, a small German town near Hanover. After considerable experience as a country practitioner, he removed to Hanover, where he acquired an extensive practice. He was a very learned man—in addition to his native German, he was proficient in French, Swedish and Latin. His medical contributions were written in Latin, but, as was the custom with physicians of that time, he also wrote poems, prose and fables in German. His most outstanding medical work was that on purpura haemorrhagica, but he also wrote on the ancient history of smallpox and on remittent fever. His original description of morbus maculosus, which is characterized by hemorrhages from the mucous membranes into the skin and vomiting of blood, has never been controverted, although additions have been made to his classic description and other forms of purpura have been described. Thus Werlhof is given the credit of having originally described a disease, which he reported accurately, and he has left for all time a written record of his valuable observations.

If the members will permit me to speak for a moment in a lighter vein, I should like to refer to an incident which illustrates the social and domestic life of the physician of the eighteenth century. When Werlhof married for the second time he was a man of means, lived in a beautiful home and had a fine estate. His home was not like that of the physician of the present day, with old magazines and papers on the table in the reception room. His house was large, and the room where patients waited for him was luxuriously furnished with magnificent black walnut furniture upholstered in red velvet, a Venetian mirror and a chandelier of rock crystal—it was all very elegant. On the day of his marriage on the ground floor two tables were set, one with twenty-five covers for his servants and their friends and another with twenty-five covers for the pensioners of the family. Each person received 2 gulden from the bridegroom. Frau Sarah, the bride, gave each servant a coin with a ring. Evidently Werlhof was a nonconformist and did

not believe in all the customs of his day. The rule was that the bridegroom should wear a long red coat, but he wore one of violet velvet. The ceremony took place, and everyone had a gay time. Delicious wine flowed in abundance. Werlhof was a great friend of Albrecht von Haller, who attended the ceremony. The coachman's father became extremely intoxicated and had to be carried from the room. Von Haller's valet, an Italian, made grimaces to attract the attention of the bride's waiting-maid and was thrown out. Von Haller read the wedding poem, the epithalamium, and musicians sang and played gleeful music in the courtyard.

His "Opera Medica" was published in Latin, compiled from notes collected by Wichmann, Werlhof's literary editor.

The next great personality in the elucidation of purpura was Johan Lukas Schönlein, who was born in 1793 and died in 1864. He was a student at Göttingen, Jena and Würzburg and became privat-docent at the University of Würzburg. He was later called to the University of Zurich to become professor of medicine and reached high eminence as a medical teacher and practitioner. There had been no one like Schönlein in Zurich. He remained there for eight years and finally left because of the solicitations of Johannes Müller, who was to Germany what Bichat was to France and Rokitansky to Austria. Johannes Müller was the foremost German scientist of his period. He was a physiologist, pathologist and biologist and a pioneer in the natural sciences. Responding to Müller's call, Schönlein went to Berlin and assumed the chair of medicine at the Charité. He made far-reaching changes and insisted on the use of German instead of Latin in his clinics and lectures. He introduced the methods of Laennec and Skoda, emphasized physical diagnosis and clinical medicine, and among other things described what he called another form of purpura—peliosis rheumatica. This was a different condition from the purpura described by Werlhof, and Schönlein recognized this fact. Peliosis rheumatica is associated with swelling about the joints, some fever and scattered purpuric spots, principally on the extremities. They are usually small and not elevated above the skin, and the eruptions occur in crops. Schönlein said that the absence of purpuric spots in the mouth, as well as hemorrhages from the mucous membranes, differentiates this variety of purpura from purpura haemorrhagica.

The next advance in the subject of purpura must be credited to Edward Heinrich Henoch, who was born in 1820 and lived until 1910. He was a distinguished person and the first great pediatrician in Germany. He established a private pediatric clinic in his own home. Later he was called to the Charité to teach children's diseases, and finally he became professor of pediatrics. He had been a student of Schönlein and became an assistant in the neurologic clinic of his uncle, the great Romberg. He went to England and France for clinical study and became the leading pediatrician of Europe. He translated Charles West's "Lectures on Diseases of Children" into German. West's treatise was the leading text in English. In 1874, Henoch described a form of purpura characterized by pain in the abdomen, bloody stools, vomiting and fever. He found that this condition was sometimes associated with rheumatoid pain and rheumatoid swelling, and consequently the form which he described may be associated with the peliosis rheumatica of Schönlein. Thus, the two conditions sometimes occur in the same patient and the resultant condition has come to be designated as the Schönlein-Henoch form purpura haemorrhagica.

Moritz Litten (1845-1907), a distinguished German clinician, is celebrated for having first called attention to the mesenteric infarcts with hemorrhage from the bowels, pulmonary infarcts and malignant endocarditis (Litten's disease), and he wrote many important papers on other subjects. He also described what is now called Litten's sign in pleurisy with effusion. He had unusual advantages in his medical training. He was assistant to Cohnheim in pathology, and, later, assistant to the celebrated Frerichs in the Berlin clinic, in 1876. In 1884, he was made professor of medicine in Berlin. Litten was known as a unitarian in the matter of purpura. He was not interested in the different types of purpura described by

Schönlein and Henoch. He thought that there was only one main variety, which was purpura haemorrhagica, and that all the other types were variations of the form which Werlhof had described as morbus maculosus.

Intimately associated with the subject of purpura, as Dr. Myers told us, is the development of present knowledge of blood platelets. Donné, in 1842, first noticed what he called the third corpuscle of the blood, the platelet. The platelets were later observed by Max Schulze and were more fully described by Sir William Osler in 1873 and later by Bizzozero, in 1883. In 1877, Georges Hayem, a professor of therapeutics and clinical medicine in the University of Paris, recognized the platelets, but he called them hematoblasts because he thought that they represented a stage in the development of red blood corpuscles. Hayem was an excellent clinician and hematologist, and he found that the platelets had much to do with clotting, and that they function as formers of fibrin in coagulation of the blood. He was among the first to describe the retractility of the clot in purpura haemorrhagica.

Denys, in 1889, made the observation that neither the red cells nor the white cells undergo any changes in purpura haemorrhagica, but that the blood platelets are diminished in number.

W. W. Duke, who was born in 1883 and graduated from Johns Hopkins University in 1903, has made some important contributions on purpura haemorrhagica. He was the first to describe the bleeding time in this disease and noted that it is prolonged. On the other hand, the coagulation time is usually normal. Duke also noted that the platelets are markedly diminished in number in this disease.

E. Glanzmann, privat-docent in the University of Bern, made important contributions. He stated that the Schönlein-Henoch purpuras are anaphylactoid. Why they are anaphylactoid and whether perhaps a toxin produces the anaphylactic substance are not known. Osler suspected the nature of the reaction when he wrote his splendid paper "The Visceral Complications of the Erythema Group", which is a classic in medical literature and describes a condition which is related to what Glanzmann afterward described as anaphylactic purpura. Glanzmann thinks that the Schönlein-Henoch purpuras are anaphylactic reactions to infectious processes.

E. Frank, professor of internal medicine in the University of Breslau, has contributed a great deal to the German literature on purpura haemorrhagica. He designated this disease as essential thrombopenia. He explained the thrombopenia as due to a defect in the function of the bone marrow, while Glanzmann thought that it is due to the disappearance of the megakaryocytes. In Frank's classification the main varieties of idiopathic morbus maculosus Werlhofii are: those in which there is intermittent or chronic thrombopenia and those which are on the borderline of aplastic anemia. Frank has stated that a normal intact capillary will not permit diapedesis or hemorrhage, with resultant purpura. According to him, purpura cannot occur unless there is damage to the wall of the vessel or at least increased porosity of the capillaries.

Paul Kaznelson, privat-docent at the University of Prague, has made many contributions on the subject of the platelet count, and he was the first to advise splenectomy in purpura haemorrhagica (1916). Following one of his first splenectomies, that on a woman who suffered from morbus maculosus, the platelet count increased and the hemorrhages stopped. For ten years she had suffered from severe hemorrhages and a maximal thrombopenia. It has been said that the bone marrow is the cradle of the platelets and the spleen their grave. Since 1916 splenectomy has been widely done, with results such as Dr. Myers indicated, sometimes perhaps not so favorable.

Dr. Myers raised a number of questions, one of which was the possible relation between the spleen and the platelets. It has been said that the spleen acts as a thrombolytic organ. It has also been thought that the spleen exerts a hormonal influence on the bone marrow, regulating the production of red cells and platelets. The successful result of splenectomy in morbus Werlhofii has been interpreted as a diminished influence or an inhibitory effect on the bone marrow.

I am sure that I may speak for every one who has heard Dr. Myers' interesting and instructive address when I say that we are pleased to have been here and happy that he came to us.

DR. BERNARD MYERS: I wish to thank the members for the kindness with which you have received me and for the very patience with which you have listened. I am sure that you do not agree with everything I have said, nor could I expect you to.

It has been to me a matter of extraordinary joy to hear Dr. Abt. I think that you do not know what Dr. Abt's name means in England. It is a name to conjure with, and now I can say that I have heard him speak and can be happy the rest of my life. I hoped that he would express an opinion that the capillaries are not primarily at fault, but I think that out of the kindness of his heart he does not wish to lead an argument which may perhaps be fatal to my theory. It has been delightful to hear Dr. Abt speak of the celebrated persons who have worked on this disease, and I shall long remember his speech.

Book Reviews

Diffuse Sclerosis. By L. Bouman, M.D. Price, $5. Pp. 160, with 68 illustrations. Baltimore: Williams & Wilkins Company and Bristol: John Wright & Sons, Ltd., 1934.

In this monograph of moderate length Bouman has formulated an extremely able and balanced presentation of his subject as it stands today. In a sense diffuse sclerosis is a disease of rather recent recognition, dating from the precise histopathologic description given by Schilder in 1912. But with attention so sharply focused, many reports have appeared since then, and all the more important of these, together with the older observations, are surveyed in this work. It is gratifying to note that the author employs the older and less committal term "diffuse sclerosis" rather than the term "encephalitis periaxialis diffusa" conferred on the disease by Schilder.

It is Bouman's prime purpose to discover by his analysis some sort of order in what has been the greatest diagnostic confusion concerning this disease. To this end he has drawn on the data of some hundred cases, including the original and notable contribution of six of his own, in five of which careful anatomic studies were made. To date diagnosis has not often been made during life, except by exclusion or as a secondary possibility. As Bouman points out, the immediate practical importance of clarifying this difficulty lies in the prevention of unnecessary operations on the brain, as tumor is perhaps the most common erroneous diagnosis.

The cases are divided into two groups: those occurring in children and those occurring in adolescents and adults, the latter being far more numerous than is often supposed. In children the appearance of psychic symptoms, disturbances of gait and convulsions on a previously normal background, progressing to marked bilateral spastic disturbances and dementia, are highly suggestive. In adults character and behavior disorders with mild deterioration are commonly the initial symptoms and are associated with bilateral spastic signs in the motor system, ordinarily not as marked as those seen in children. In both groups cortical blindness is often present, frequently early, and is of great help in suggesting the diagnosis. This feature, however, may be lacking. A disconcerting variability in the picture is recognized, and while Bouman is optimistic about the possibilities of more accurate diagnosis, he does not fall into the error of defining too rigid and definite a syndrome, as has been done by others. A full discussion of the differential diagnosis is given, which in adults includes principally multiple sclerosis and tumor of the brain and, in children, Pelizaeus-Merzbacher's disease, amaurotic family idiocy, tuberous sclerosis, encephalitis of various sorts, Little's disease, familial infantile diplegia and juvenile paresis.

Not the least merit of the work lies in the portion devoted to pathologic anatomy. As has been mentioned, much of this is the author's own work, and the numerous photomicrographs are very good. In spite of the accurate descriptions, many questions of pathogenesis and etiology remain moot. The inflammatory nature of the disease in some of the cases and its close relationship to disseminated sclerosis in others and to the heredodegenerations in still others are brought out. The only conclusion permissible at present would seem to be that this condition is not a disease sui generis, but a morbid anatomic state capable of being produced by a variety of influences damaging the myelinated fiber systems chiefly.

Tuberculosis in the Child and the Adult. By Francis Marion Pottenger, M.D., LL.D., F.A.C.P., Clinical Professor of Medicine (Department of Chest), University of Southern California School of Medicine; Medical Director, the Pottenger Sanatorium and Clinic for Diseases of the Chest, Monrovia, Calif. Cloth. Price, $8.50. Pp. 590, with 85 illustrations. St. Louis: C. V. Mosby Company, 1934.

As the author states, he has discussed in a compact volume the leading facts about tuberculosis as they have been discovered in recent years and as he has

interpreted them in his practice, with a view especially to the needs of students and younger practitioners. The development and course of primary tuberculosis according to modern concepts are described. On the moot point of the relative importance of allergy or resistance in overcoming infection Pottenger favors the school of thought which attributes more benefit to allergy than is conceded by many authorities. Much space is given to a consideration of various reflex effects of disease of the lung and the physiologic concepts of visceral neurology. It is to be questioned whether many practitioners will be able to emulate the author's skill in determining minor differences in muscle tone and texture, but at least they can learn his methods. The sections on clinical tuberculosis, profusely illustrated with roentgenograms, show the touch of a clinician of vast experience and will be of value to general practitioners of any age. In the description of the use of tuberculin in diagnosis it might seem that hardly enough emphasis has been laid on the possible dangers of using the subcutaneous route. For inexperienced practitioners the percutaneous or intracutaneous methods are preferable. Twenty per cent of the text is allocated to treatment. This section contains valuable advice for all who lack the experience necessary in forming judgment.

Child Guidance Clinics. By Dr. George S. Stevenson and Geddes Smith. Price, $1.50. Pp. 186. London: Oxford University Press; New York: The Commonwealth Fund, 1934.

Twenty-five years have passed since the first child guidance clinic was established in Chicago. At present there are more than two hundred such clinics in this country. In this book Stevenson and Smith first give the history of the evolvement of these clinics, sometimes spoken of as the mental hygiene movement. After describing the general scientific background and the popular demand for such clinics, they describe the early clinics, especially the demonstration clinics sponsored by the National Committee for Mental Hygiene. The early failures and successes of each clinic are discussed. Succeeding chapters deal with the methods used in mental hygiene clinics, the place, need and function of such clinics in a community and their relationship to the practice of medicine.

The book is of value because it is the first history of mental hygiene clinics. It is historically somewhat inaccurate in not giving sufficient credit to the clinics other than those sponsored by the National Committee for Mental Hygiene. It is particularly valuable, however, in pointing out the errors of the clinics that have developed and in indicating the most efficient way of establishing clinics of this kind in the future. It is interestingly written and would be particularly valuable to those who are interested in the development of psychiatric treatment of children.

L'eczéma du nourrisson. By M. Péhu and R. Aulagnier. Price, 25 francs. Pp. 164. Paris: Gauthier-Villars & Cie, 1934.

The old and the new conceptions of infantile eczema are considered and compactly presented in this monograph. Of the many theories concerning the etiology of infantile eczema, the authors favor the view that an allergic constitution is the fundamental cause. It is considered important to limit sharply the diagnosis of eczema and to differentiate it clearly from other cutaneous manifestations in infants. The general clinical course and complications of eczema are discussed; the tendency to unexpected death and the relation of eczema to other allergic conditions are considered, and experimental results and laboratory tests employed in the study of eczema are analyzed and evaluated. The common mistakes made in managing eczematous infants are mentioned. The last two chapters deal with treatment, both general and local. Many prescriptions for use in the various stages of eczema are suggested. The present day knowledge of eczema in infants is well reviewed and presented from a practical, clinical point of view of value to practitioners who have to deal with this problem. An extensive bibliography is included.

Directory of Pediatric Societies *

INTERNATIONAL

International Association of Preventive Pediatrics

President: Professor G. Scheltema, 6a Heereplein, Groningen, The Netherlands.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.
Place: Bâle, Switzerland: Time: September 1935.

FOREIGN

British Paediatric Association

President: Dr. Hugh Thursfield, 84 Wimpole St., London, W. 1.
Secretary: Dr. Arthur G. Maitland Jones, 31 A Weymouth St., London, W. 1.
Place: Newcastle, County Down, Ireland. Time: May 3-4, 1935.

Royal Society of Medicine, Section for the Study of Disease in Children

President: R. C. Jewesbury, Esq., M.D., 5 Wimpole St., London, W. 1.
Secretary: Dr. Helen Mackay, 28 John St., London, W. C. 1.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:30 p. m.

NATIONAL

American Medical Association, Scientific Assembly, Section on Diseases of Children

Chairman: Dr. A. Graeme Mitchell, Children's Hospital, Cincinnati.
Secretary: Dr. Ralph M. Tyson, 334 S. 21st St., Philadelphia.
Place: Atlantic City, N. J. Time: June 10-14, 1935.

American Academy of Pediatrics

President: Dr. Thomas B. Cooley, 1728 Seminole Ave., Detroit.
Secretary: Dr. C. G. Grulee, 636 Church St., Evanston, Ill.
Place: New York. Time: June 7-8, 1935.
Region I. Place: Philadelphia. Time: Oct. 11-12, 1935.
Regions II and III. Place: St. Louis. Time: Fall, 1935.
Region IV. Place: Seattle. Time: Fall, 1935.

American Child Health Association

President: Dr. Samuel McC. Hamill, 1822 Spruce St., Philadelphia.
Secretary: Dr. Philip Van Ingen, 125 E. 71st St., New York.

American Hospital Association, Children's Hospital Section

President: Mr. Robert Witham, Children's Hospital, Denver.
Secretary: Miss Agnes O'Roke, Kosair Crippled Children's Hospital, Louisville, Ky.

American Pediatric Society

President: Dr. Borden S. Veeder, 3720 Washington Ave., St. Louis.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid St., St. Louis.
Place: Wade Park Manor, Cleveland. Time: May 2-4, 1935.

Canadian Society for the Study of Diseases of Children

President: Dr. D. P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary-Treasurer: Dr. R. R. Struthers, 1414 Drummond St., Montreal.
Place: Buffalo, N. Y. Time: June 1935.

Society for Pediatric Research

President: Dr. Joseph Stokes Jr., Children's Hospital, Philadelphia.
Secretary: Dr. A. A. Weech, Babies Hospital, New York.
Place: Atlantic City, N. J. Time: May 1935.

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* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

SECTIONAL

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. Armin Rembe, Stimson Bldg., Seattle.
Secretary: Dr. Frank H. Douglass, 1227 Medical and Dental Bldg., Seattle.

SOUTHERN MEDICAL ASSOCIATION, SECTION ON PEDIATRICS

Chairman: Dr. Oliver W. Hill, 301 Medical Arts Bldg., Knoxville, Tenn.
Secretary: Dr. Madison Hines Roberts, 104 Ponce de Leon Ave., N. E., Atlanta, Ga.

STATE

ALABAMA PEDIATRIC SOCIETY

President: Dr. Charles Abbott, 1817 Broad St., Tuscaloosa.
Secretary-Treasurer: Dr. Wallace Clyde, Employees' Hospital, Fairfield.
Place: Mobile. Time: April 17-19, 1935.

GEORGIA PEDIATRIC SOCIETY

President: Dr. Benjamin Bashinski, 700 Spring St., Macon.
Secretary-Treasurer: Dr. Roger W. Dickson, 33 Ponce de Leon Ave., N. E., Atlanta.

INDIANA STATE PEDIATRIC SOCIETY

President: Dr. Lonis H. Segar, 23 E. Ohio St., Indianapolis.
Secretary-Treasurer: Dr. Matthew Winters, 23 E. Ohio St., Indianapolis.
Time: Two meetings a year.

LOUISIANA STATE PEDIATRIC SOCIETY

President: Dr. John Signorelli, 2000 Tulane Ave., New Orleans.
Secretary-Treasurer: Dr. Edwin A. Socola, 1027 Canal Bank Bldg., New Orleans.
Place: New Orleans. Time: April 29, 1935.

MEDICAL SOCIETY OF STATE OF NEW YORK, SECTION ON PEDIATRICS

Chairman: Dr. George Sincerbeaux, 6 William St., Auburn.
Secretary: Dr. John D. Craig, 12 E. 11th St., New York.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Edgar E. Martmer, 749 David Whitney Bldg., Detroit.
Secretary: Dr. C. R. Dengler, 131 W. Michigan Ave., Jackson.
Place: Flint. Time: September 1935.

MISSISSIPPI STATE PEDIATRIC SOCIETY

President: Dr. N. C. Womack, Jackson Infirmary, Jackson.
Secretary-Treasurer: Dr. Guy C. Jarratt, 920 Crawford St., Vicksburg.
Place: To be designated by Society. Time: Yearly.

NEBRASKA PEDIATRIC SOCIETY

President: Dr. J. A. Henske, 1614 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. J. H. Murphy, 915 Medical Arts Bldg., Omaha.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. J. Buren Sidbury, 15 N. Fifth St., Wilmington.
Secretary: Dr. E. K. McLean, 121 W. Seventh St., Charlotte.
Place: Various children's hospitals. Time: Twice a year.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. C. V. Rice, 222 Wall St., Muskogee.
Secretary: Dr. B. H. Nicholson, 301 N. W. Twelfth St., Oklahoma City.
Place: Oklahoma City. Time: May 1935.

PENNSYLVANIA MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Francis T. O'Donnell, 345 North Main St., Wilkes-Barre.
Secretary: Dr. Theodore O. Elterich, 119 S. Highland Ave., Pittsburgh.
Place: Harrisburg. Time: Sept. 30-Oct. 3, 1935.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Julian P. Price, Medical Bldg., Florence.
Secretary-Treasurer: Dr. Leland B. Salters, 317 S. Warley Ave., Florence.
Place: Columbia. Time: Feb. 18, 1935.

TENNESSEE STATE PEDIATRIC SOCIETY

President: Dr. Arthur G. Jacobs, 1193 Madison Ave., Memphis.
Secretary: Dr. Joe T. Smith, 702 Medical Arts Bldg., Knoxville.
Place: Nashville. Time: April 1935.

TEXAS PEDIATRIC SOCIETY

President: Dr. Ramsay H. Moore, 3600 Fairmount St., Dallas.
Secretary-Treasurer: Dr. F. H. Lancaster, Medical Arts Bldg., Houston.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. W. P. McDowell, 142 W. York St., Norfolk.
Secretary: Dr. W. A. McGee, 616 W. Grace St., Richmond.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. R. C. Hood, 428 W. Pike St., Clarksburg.
Secretary: Dr. Russell C. Bond, 1325 Chapline St., Wheeling.

LOCAL

ACADEMY OF MEDICINE OF BROOKLYN, PEDIATRIC SECTION

President: Dr. Harry M. Greenwald, 499 Ocean Ave., Brooklyn.
Secretary: Dr. Sylvan D. Lazarus, 847 Lincoln Place, Brooklyn.
Place: Medical Society of County of Kings Bldg., 1313 Bedford Ave., Brooklyn.
Time: Third Wednesday of each month from October to May, 8:30 p. m.

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. J. A. Garvin, Carnegie Medical Bldg., Cleveland.
Secretary: Dr. William M. Champion, 2323 Prospect Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. C. V. Mulligan, 17 Walmer Rd., N., Toronto.
Secretary: Dr. T. B. Verner, 170 St. George St., Toronto.

BRONX PEDIATRIC SOCIETY

President: Dr. Harry M. Shapiro, 1882 Grand Concourse, New York.
Secretary: Dr. Daniel J. Dolan, 420 E. 159th St., New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

BROOKLYN ACADEMY OF PEDIATRICS

President: Dr. W. F. Watton, 240 Berkeley Pl., Brooklyn.
Secretary: John A. Monfort, 861 Carroll St., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Fourth Wednesday of each month, except May, June, July, August and September.

CENTRAL NEW YORK PEDIATRIC CLUB

President: Dr. Frank Vander Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Thursday of April and September.

CHICAGO PEDIATRIC SOCIETY

President: Dr. Stanley Gibson, 9503 Prospect Ave., Chicago.
Secretary: Dr. James H. Wallace, 715 Lake St., Oak Park, Ill.
Place: John B. Murphy Memorial Bldg. Time: Third Tuesday of each month.

DALLAS COUNTY PEDIATRIC SOCIETY

President: Dr. P. E. Luecke, 4105 Live Oak St., Dallas, Texas.
Secretary: Dr. R. S. Usry, 1835 Garrett Ave., Dallas, Texas.
Place: Bradford Memorial Hospital. Time: 1 p. m., first and third Saturdays of each month.

DETROIT PEDIATRIC SOCIETY

President: Dr. Earl W. May, 1551 Woodward Ave., Detroit.
Secretary: Dr. E. A. Wishropp, 10 Peterboro Ave., Detroit.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month.

FULTON COUNTY MEDICAL SOCIETY, PEDIATRIC SECTION (ATLANTA, GA.)

Chairman: Dr. Joseph Yampolsky, 478 Peachtree St., Atlanta.
Secretary: Dr. T. I. Willingham, 384 Peachtree St., Atlanta.
Place: Academy of Medicine, 38 Prescott St., N. E. Time: Second Thursday of each month from October to April, 8 p. m.

HOUSTON PEDIATRIC SOCIETY

President: Dr. Frank Lancaster, Medical Arts Bldg., Houston, Texas.
Secretary-Treasurer: Dr. A. A. Little Jr., 817 Holman Ave., Houston, Texas.
Place: Houston Club: Time: Third Monday of each month.

INTERMOUNTAIN PEDIATRIC SOCIETY

President: Dr. Helmina Jeidell, 11 Exchange Pl., Salt Lake City, Utah.
Secretary-Treasurer: Dr. Edwin R. Murphy, 9 Exchange Pl., Salt Lake City, Utah.
Place: Salt Lake City, General Hospital. Time: First Thursday of each month, 8 p. m.

KANSAS CITY (MISSOURI) PEDIATRIC SOCIETY

President: Dr. Harry M. Gilkey, 1103 Grand Ave., Kansas City.
Secretary: Dr. S. A. Stadler, 6133 Brookside Blvd., Kansas City.
Place: Kansas City General Hospital. Time: On call.

MEDICAL SOCIETY OF THE COUNTY OF QUEENS, INC., SECTION ON PEDIATRICS

Chairman: Dr. Henry A. Reisman, 148, 88th Ave., Jamaica, L. I.
Secretary-Treasurer: Dr. Edith A. Mittell, 112 Queens Blvd., Forest Hills, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y.: Time: Third Monday of October, January, March and May.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. Harry J. Jacobson, 1193 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Clyde V. Croswell, 1052 Madison Ave., Memphis, Tenn.
Place: Memphis General Hospital. Time: Second Tuesday of each month, except June, July and August, 8 p. m.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. J. Gurney Taylor, 324 E. Wisconsin St., Milwuakee.
Secretary: Dr. H. B. Miner, 425 E. Wisconsin Ave., Milwaukee.
Place: Children's Hospital. Time: Second Wednesday of each alternate month, beginning with February.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. Paul Emerson, 319 Longwood Ave., Boston.
Secretary-Treasurer: Dr. Henry E. Gallup, 66 Commonwealth Ave., Boston.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

NEW YORK ACADEMY OF MEDICINE, SECTION OF PEDIATRICS

Chairman: Dr. Harry Bakwin, 132 E. 71st St., New York.
Secretary: Dr. Alexander T. Martin, 107 E. 85th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

NORTHWESTERN PEDIATRIC SOCIETY

President: Dr. O. W. Rowe, 205 W. 2nd St., Duluth, Minn.
Secretary: Dr. E. F. Robb, 1801 Lyndale Ave., S., Minneapolis.
Place: Minneapolis. Time: Spring, 1935.

PHILADELPHIA PEDIATRIC SOCIETY

President: Dr. John D. Donnelly, 115 Bryn Mawr Ave., Bala, Pa.
Secretary: Dr. James E. Bowman, 4091 Comly St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to June, inclusive.

PITTSBURGH PEDIATRIC SOCIETY

President: Dr. Carl K. Wagener, Jenkins Arcade, Pittsburgh.
Secretary-Treasurer: Dr. E. R. McClusky, 3200 Fifth Ave., Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Tuesday, alternate months from October to April, inclusive.

RICHMOND PEDIATRIC SOCIETY

President: Dr. W. A. McGee, 616 W. Grace St., Richmond, Va.
Secretary-Treasurer: Dr. Emily Gardner, 1100 W. Franklln St., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: First Thursday of each month (except July, August and September).

ROCHESTER PEDIATRIC SOCIETY

President: Dr. H. F. Rowley, 176 S. Goodman St., Rochester, N. Y.
Secretary: Dr. J. M. Parker, 26 S. Goodman St., Rochester, N. Y.
Place: Arranged by program committee. Time: Second Friday of each month.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. Ralph Verploeg, 1850 Gilpin St., Denver.
Secretary: Dr. Max M. Ginsburg, Metropolitan Bldg., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 2:30 p. m.

ST. LOUIS PEDIATRIC SOCIETY

President: Dr. J. V. Cooke, St. Louis Children's Hospital, St. Louis.
Secretary-Treasurer: Dr. Katherine Bain, Beaumont Bldg., St. Louis.
Place: St. Louis Medical Society. Time: Third Friday of every month.

SEATTLE PEDIATRIC SOCIETY

President: Dr. Arthur E. Wade, 1215, 4th Ave., Seattle.
Secretary: Dr. Walter B. Seelye, Cobb Bldg., Seattle.
Place: College Club. Time: Third Friday of each month, 6:30 p. m.

SOUTHWESTERN PEDIATRIC SOCIETY

President: Dr. Victor E. Stork, 1136 W. Sixth St., Los Angeles.
Secretary: Dr. Howard R. Cooder, 3875 Wilshire Blvd., Los Angeles.
Place: University Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

UNIVERSITY OF MICHIGAN PEDIATRIC AND INFECTIOUS DISEASE SOCIETY

President: Dr. Daniel Budson, 3001 W. Grand Blvd., Detroit.
Secretary: Dr. D. Murray Cowie, University of Michigan, Ann Arbor, Mich.
Place: Ann Arbor, Mich. Time: Nov. 22-23, 1935.

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